Glutamine metabolic reprogramming remodels the immunosuppressive microenvironment and modulates immunotherapy response in renal cell carcinoma (Review)

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Abstract. Clear cell renal cell carcinoma (ccRCC) is characterized by profound metabolic reprogramming, with glutamine addiction emerging as a central hallmark that extends beyond supporting tumor proliferation. This review synthesizes current knowledge on how glutamine metabolic reprogramming remodels the immunosuppressive tumor microenvironment and modulates immunotherapy response in renal cell carcinoma. The molecular basis of glutamine addiction is discussed, focusing on the von Hippel-Lindau/hypoxia-inducible factor axis, MYC activation and epigenetic regulation. The mechanisms by which glutamine metabolism orchestrates immune evasion are examined, including tumor immune cell competition, impaired effector T-cell function, expansion of immunosuppressive populations such as regulatory T cells and M2 polarized macrophages, and upregulation of immune checkpoints. Therapeutic strategies targeting glutamine metabolism, from transporter and glutaminase inhibition to dietary restriction, are summarized along with mixed clinical trial outcomes that underscore the need for patient selection. Candidate predictive biomarkers across genetic, metabolic, immune and imaging domains are also reviewed. This review aims to provide an integrated framework for understanding glutamine-driven immune modulation and to guide future therapeutic development in ccRCC.

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Abbreviations: BAP1, BRCA1-associated protein 1; CAFs, cancer-associated fibroblasts; ccRCC, clear cell renal cell carcinoma; CSCs, cancer stem cells; CTLA-4, cytotoxic T lymphocyte-associated protein 4; ECM, extracellular matrix; EMT, epithelial-mesenchymal transition; FTO, fat mass and obesity-associated protein; GLS1, glutaminase 1; HIF, hypoxia-inducible factor; ICIs, immune checkpoint inhibitors; IL-23, interleukin-23; LAG-3, lymphocyte activation gene-3; MDSCs, myeloid-derived suppressor cells; MRS, magnetic resonance spectroscopy; mTOR, mammalian target of rapamycin; PD-L1, programmed death-ligand 1; PET, positron emission tomography; PBRM1, polybromo-1; PYCR1, pyrroline-5-carboxylate reductase 1; RCC, renal cell carcinoma; SDHB, succinate dehydrogenase subunit B; SETD2, SET domain-containing protein 2; SLC1A5, solute carrier family 1 member 5; also known as ASCT2; TAMs, tumor-associated macrophages; TCA, tricarboxylic acid; TET2, ten-eleven translocation 2; TKI, tyrosine kinase inhibitor; TME, tumor microenvironment; Tregs, regulatory T cells; VEGF, vascular endothelial growth factor; VHL, von Hippel-Lindau

Key words: renal cell carcinoma, glutamine metabolism, metabolic reprogramming, glutamine addiction, immunosuppressive microenvironment, immune checkpoint, immunotherapy response, tumor microenvironment

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1. Introduction

Renal cell carcinoma (RCC) represents one of the most common malignancies of the urinary system, with clear

cell RCC (ccRCC) accounting for ~75-80% of all cases (1). Given marked metabolic differences among RCC subtypes, this review focuses primarily on ccRCC; unless otherwise specified, 'RCC' hereafter refers to ccRCC and evidence from non-clear cell subtypes is explicitly identified. Despite significant advances in therapeutic strategies over the past decade, advanced RCC remains a major clinical challenge due to its intrinsic resistance to conventional chemotherapy and radiotherapy. The introduction of immune checkpoint inhibitors (ICIs) has revolutionized the treatment landscape for metastatic RCC, yet primary and acquired resistance continue to limit durable clinical responses in a substantial proportion of patients (2,3). Understanding the mechanisms that underpin immunotherapy resistance has therefore become a critical priority for improving patient outcomes.

Metabolic reprogramming is now widely recognized as a hallmark of cancer that extends beyond the classical Warburg effect. In ccRCC, the metabolic landscape is uniquely shaped by frequent inactivation of the von Hippel-Lindau (VHL) tumor suppressor gene, which leads to constitutive activation of hypoxia-inducible factors and extensive rewiring of cellular metabolism (2,4). Wettersten *et al* (5) demonstrated through combined proteomics and metabolomics analysis that metabolic alterations in ccRCC are closely linked to tumor grade, suggesting that progressive metabolic dysregulation drives disease aggressiveness. Beyond glucose metabolism, emerging evidence has highlighted the critical importance of amino acid reprogramming in ccRCC progression. A growing body of literature has established that ccRCC cells exhibit a remarkable dependency on exogenous glutamine, a condition often termed 'glutamine addiction' (6,7).

Glutamine serves as a key nitrogen and carbon source that supports nucleotide biosynthesis, redox homeostasis, and anaplerotic entry into the tricarboxylic acid (TCA) cycle. In ccRCC, this metabolic dependency is driven by multiple oncogenic signalling pathways. Shroff *et al* (8) provided compelling evidence that MYC oncogene overexpression drives RCC in a mouse model specifically through glutamine metabolism, establishing a causal link between oncogene activation and metabolic vulnerability. Subsequent work has revealed that the VHL-hypoxia-inducible factor (HIF) axis exerts complex, context-dependent effects on glutamine utilisation, with recent findings indicating that HIF2α actually inhibits mitochondrial glutaminase clustering to sustain tumor growth, challenging the simplistic view that HIF simply promotes glutaminolysis (9). These observations underscore the intricate and at times counterintuitive nature of metabolic regulation in ccRCC.

The tumor microenvironment (TME) of ccRCC is characterised by profound immune suppression, which limits the efficacy of ICIs. Importantly, glutamine metabolism is increasingly recognised as a critical determinant of both tumor cell behaviour and immune cell function within the TME. Fu *et al* (10) elucidated that tumor-associated macrophage-derived interleukin (IL)-23 links kidney cancer glutamine addiction with immune evasion, demonstrating a direct mechanistic connection between tumor metabolic reprogramming and suppression of anti-tumor immunity. Furthermore, Wei *et al* (11) showed that pyrroline-5-carboxylate reductase 1 (PYCR1) regulates glutamine metabolism to construct an immunosuppressive microenvironment that promotes ccRCC progression, highlighting how metabolic enzymes can shape immune cell composition. Wu *et al* (12) subsequently deciphered glutamine metabolism patterns associated with malignancy and TME composition, revealing that high glutamine metabolic activity correlates with reduced infiltration of activated $CD8^+$ T cells and enrichment of immunosuppressive populations.

The therapeutic potential of targeting glutamine metabolism in RCC has garnered substantial interest. Okazaki *et al* (13) demonstrated that glutaminase inhibition suppresses pyrimidine synthesis and induces growth arrest in VHL-deficient renal cancers, providing preclinical proof-of-concept for this approach. Clinical translation has progressed with the development of the glutaminase inhibitor telaglenastat (CB-839), although phase II trials such as CANTATA and ENTRATA have yielded mixed results, underscoring the need for improved patient selection and combination strategies (14,15). More recently, Ma *et al* (16) provided direct evidence that inhibition of glutamine metabolism blocks tumor growth and sensitises ccRCC to immune checkpoint blockade, suggesting that combining metabolic targeting with immunotherapy may overcome resistance. Despite these advances, critical questions remain regarding the heterogeneity of glutamine dependency, the identification of predictive biomarkers and the optimal integration of metabolic agents with existing therapies (3,4).

Given the complex interplay between glutamine metabolic reprogramming, immune evasion and immunotherapy response in RCC, a comprehensive synthesis of current knowledge is urgently needed. This review aims to provide an integrated overview of the molecular mechanisms driving glutamine addiction in RCC, its role in remodelling the immunosuppressive TME and the emerging therapeutic strategies designed to exploit this metabolic vulnerability. Particular emphasis is placed on recent advances that have reshaped the understanding of how glutamine metabolism modulates immunotherapy outcomes, with the goal of informing future research directions and clinical trial design.

2. Fundamentals of glutamine metabolism in normal and cancer cells

Glutamine, the most abundant amino acid in human plasma, serves as a critical nitrogen and carbon source for numerous biosynthetic and bioenergetic pathways (17). In normal cells, glutamine homeostasis is tightly regulated to support proliferation, redox balance and inter-organ nitrogen trafficking (18). However, cancer cells frequently exhibit 'glutamine addiction', a metabolic reprogramming event that sustains rapid growth under nutrient stress (19). Understanding the fundamental differences in glutamine handling between normal and malignant cells provides the conceptual framework for targeting this pathway therapeutically. Fig. 1 compares glutamine metabolic fluxes in normal vs. cancer cells. In normal cells, glutamine uptake is basal and metabolism supports homeostasis. In cancer cells, upregulated transporters (SLC1A5) and GLS1 drive enhanced glutamine uptake, feeding into reductive carboxylation, nucleotide synthesis and redox balance. Key therapeutic targets (transporter blockade, GLS1 inhibition) are indicated.

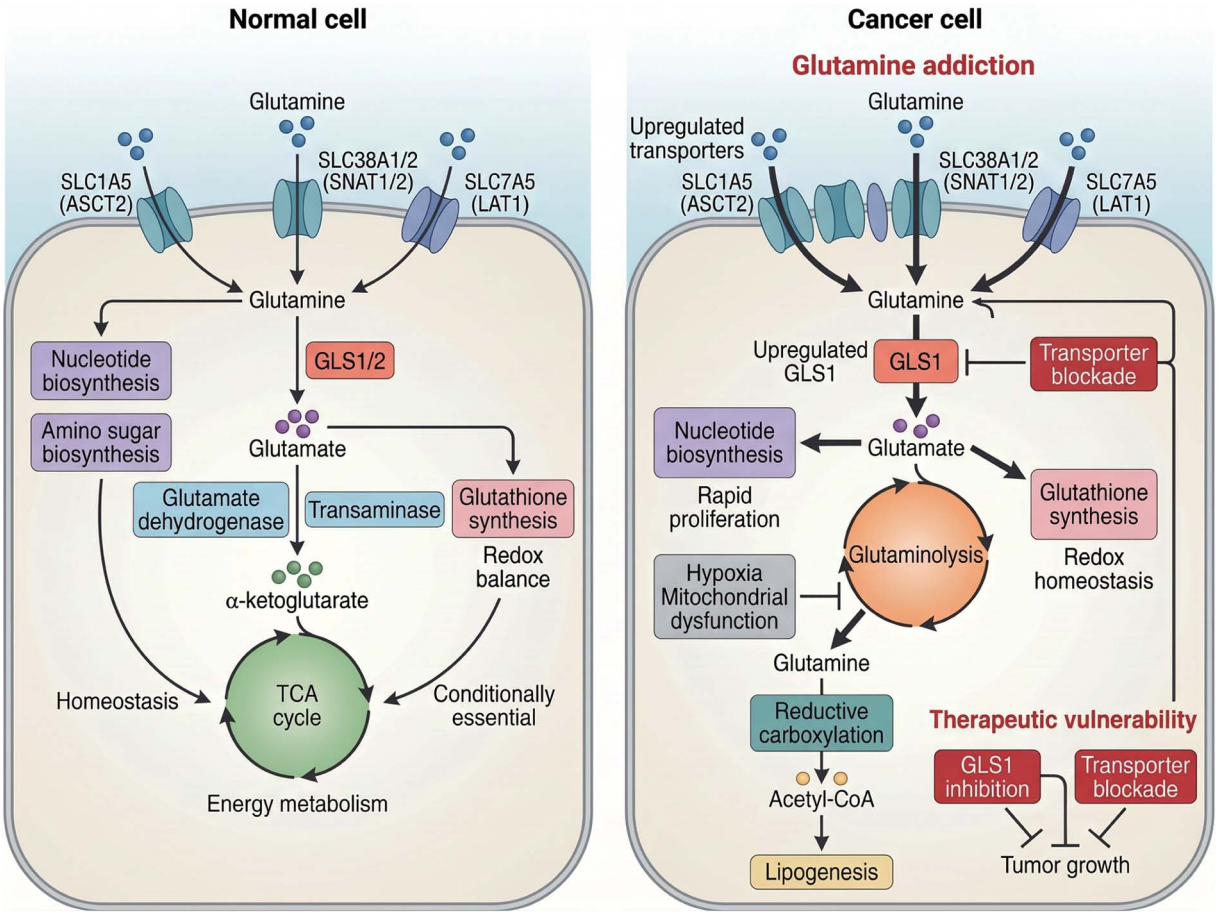


Figure 1. Schematic overview of glutamine metabolism in normal cells vs. cancer cells. In normal cells, glutamine metabolism maintains physiological homeostasis. In cancer cells, enhanced glutamine uptake (via SLC1A5, SLC38A1/2, SLC7A5) and glutaminolysis (GLS1) drive tumor proliferation, redox balance and reductive carboxylation. Key therapeutic targets (transporter blockade, GLS1 inhibition) are indicated. GLS1, glutaminase 1; SLC1A5, solute carrier family 1 member 5; TCA, tricarboxylic acid.

Glutamine metabolism in normal cells. In physiological conditions, glutamine is classified as a non-essential amino acid, as it can be synthesized from glutamate and ammonia via glutamine synthetase. However, during periods of metabolic stress or rapid cell division, glutamine becomes conditionally essential. Newsholme *et al* (20) systematically reviewed how glutamine metabolism supports optimal immune and central nervous system function, emphasizing its role in lymphocyte proliferation and macrophage phagocytosis. Normal cells utilize glutamine primarily as a nitrogen donor for nucleotide and amino sugar biosynthesis, as well as a carbon source for the TCA cycle through glutaminolysis. The initial step involves conversion of glutamine to glutamate by glutaminases (GLS1 and GLS2), followed by glutamate dehydrogenase or transaminase reactions producing α-ketoglutarate. Andersen *et al* (21) comprehensively characterized the glutamate/GABA-glutamine cycle in astrocytes, demonstrating that glutamine serves as the essential precursor for neurotransmitter glutamate and GABA, highlighting its non-metabolic signaling functions in the central nervous system. The cellular uptake of glutamine is mediated by multiple transporter families, including solute carrier family 1 member 5 (SLC1A5 or ASCT2), SLC38A1-2 (SNAT1/2) and SLC7A5 (LAT1). Bröer (22) reviewed how these amino acid transporters modulate glucose homeostasis and systemic metabolism, noting that their expression is tightly regulated by nutritional and hormonal signals. Importantly, glutamine also supports the cellular antioxidant defense system by providing glutamate for glutathione synthesis. Gong *et al* (23) comprehensively reviewed how glutamine metabolism regulates oxidative homeostasis in cancers, noting that disruption of glutamine-dependent antioxidant pathways can trigger ferroptotic cell death. Thus, in normal cells, glutamine metabolism is highly regulated and integrated with systemic physiological demands.

Glutamine addiction in cancer cells. Malignant transformation imposes profound alterations in glutamine handling, leading to a state of 'glutamine addiction' that distinguishes cancer cells from their normal counterparts. Li *et al* (24) provided a comprehensive overview of how oncogenic signaling pathways drive this addiction, noting that the dependency arises from enhanced demands for nucleotide biosynthesis, redox homeostasis and anaplerotic carbon entry into the TCA cycle. The review by Halama and Suhre (25) outlined a roadmap for advancing cancer treatment by targeting glutamine metabolism, emphasizing that the degree of addiction varies substantially across tumor types and even within individual tumors. A critical observation is that numerous cancer cells, including those with MYC or KRAS activation, become unable to survive

without exogenous glutamine despite possessing the biosynthetic capacity for endogenous production. Sharma *et al* (26) reviewed the concept of targeting glutamine metabolism by focusing on the glutaminolysis pathway, highlighting that the metabolic enzyme GLS1 is frequently upregulated in cancers and represents a viable therapeutic vulnerability.

Several interconnected mechanisms explain this heightened dependency. First, accelerated proliferation demands constant nucleotide supply, and glutamine-derived carbamoyl phosphate and formate groups are indispensable for pyrimidine and purine synthesis. Second, cancer cells frequently upregulate glutamine transporters to secure sufficient influx. Third, in hypoxic or mitochondrial-defective tumors, glutamine supports reductive carboxylation as an alternative pathway to generate acetyl-CoA for lipogenesis. Jin *et al* (27) synthesized the current understanding of targeting glutamine metabolism as a therapeutic strategy across multiple malignancies, noting that the metabolic plasticity of cancer cells often limits the efficacy of single-agent interventions. Dong *et al* (28) recently reviewed the crosstalk between glutamine metabolism and tumor immune response, emphasizing that the same pathways sustaining cancer cell survival also create a nutrient-deprived microenvironment that suppresses effector immune cells. Furthermore, the oncometabolite perspective adds another layer of complexity, as certain cancer-associated mutations produce metabolites that further rewire glutamine utilization. Zou *et al* (19) systematically reviewed targeting glutamine metabolism as a potential cancer treatment, concluding that combination strategies addressing metabolic redundancy are likely required for durable clinical responses. Collectively, these findings establish that glutamine addiction arises from convergent oncogenic signals, yet the precise mechanisms of dependency exhibit considerable heterogeneity, necessitating careful patient stratification for metabolic therapies.

3. Molecular basis of glutamine metabolic reprogramming in RCC

RCC, particularly ccRCC, exhibits profound glutamine metabolic reprogramming driven by genetic alterations and oncogenic signaling (2,4). This section delineates the molecular underpinnings, including VHL/HIF pathway dysregulation, MYC and mammalian target of rapamycin (mTOR) activation, epigenetic modifications, and the expression of glutamine transporters and metabolic enzymes. The metabolic heterogeneity within and between RCC subtypes is also discussed, providing a framework for understanding tumor progression and therapeutic vulnerabilities (29-32). Fig. 2 outlines the molecular network regulating glutamine metabolism in RCC. VHL/HIF, MYC/PI3K/AKT/mTOR complex 1 (mTORC1) and epigenetic regulators [fat mass and obesity-associated protein (FTO), ten-eleven translocation 2 (TET2)] converge to upregulate SLC1A5 and GLS1, supporting tumor growth via reductive carboxylation, glutathione synthesis, and nucleotide production. Metabolic heterogeneity and tumor–immune glutamine competition are core features.

Genetic and epigenetic drivers of glutamine addiction. The VHL tumor suppressor is inactivated in >90% of ccRCC, leading to constitutive activation of hypoxia-inducible factors HIF-1α and HIF-2α and extensive metabolic rewiring (29,30). VHL deficiency not only promotes glycolytic reprogramming but also profoundly influences glutamine metabolism. Liao *et al* (31) comprehensively reviewed how VHL/HIF signaling orchestrates metabolic adaptations in ccRCC, including the regulation of glutamine transporters and enzymes. Notably, VHL loss results in reductive stress in renal cells, which may impact glutamine-dependent redox homeostasis (32). Zhao *et al* (9) recently demonstrated that HIF2α inhibits glutaminase clustering in mitochondria, thereby restraining complete glutamine oxidation while sustaining tumor growth, a finding that challenges the notion that HIF simply promotes glutaminolysis. This regulatory logic should not be interpreted as evidence against glutamine addiction in ccRCC. Rather, HIF2α sustains glutamine dependence through alternative mechanisms, including transcriptional upregulation of glutamine transporters and anaplerotic enzymes, while simultaneously preventing excessive GLS1 clustering that would otherwise sensitize cells to glutamine deprivation-induced death. Thus, HIF2α creates a state of 'controlled glutamine addiction' that supports biosynthetic demands without triggering the vulnerability associated with unrestrained glutaminolysis (9). Mechanistically, GLS1 clustering is rapidly triggered by reduced intracellular glutamate levels and requires mitochondrial fission; clustered GLS1 exhibits markedly enhanced glutaminase activity and promotes apoptosis under glutamine-deprived conditions. HIF2α prevents this clustering independently of its transcriptional activity, thereby maintaining low GLS1 activity and shielding ccRCC cells from glutamine-deprivation-induced death. This contrasts with the conventional model in which HIF promotes glutaminolysis through transcriptional upregulation of metabolic enzymes. This mechanism also provides a plausible explanation for the limited clinical efficacy of GLS1 inhibitors in ccRCC and suggests that combining HIF2α inhibition with strategies that restore GLS1 clustering may represent a rational therapeutic approach (9). This inhibitory effect on glutaminase activity represents a metabolic adaptation that prevents excessive reactive oxygen species production. Furthermore, the oncometabolite fumarate, which accumulates in hereditary leiomyomatosis and RCC, rewires RNA methylation patterns and indirectly influences glutamine metabolic gene expression (33). Yong *et al* (29) summarized how various oncometabolites in renal cancer, including succinate and fumarate, disrupt normal metabolic sensing and contribute to glutamine dependency.

Beyond VHL, the MYC oncogene and mTORC1 signaling are critical drivers of glutamine addiction. Sainero-Alcolado *et al* (34) showed that targeting MYC induces lipid droplet accumulation in ccRCC, indicating a metabolic shift that may alter glutamine utilization. Drusian *et al* (35) demonstrated that mTORC1 upregulation in a mouse RCC model leads to accumulation of fumarate, linking mTOR activation to alterations in glutamine-dependent anaplerosis. The PI3K/AKT/mTOR pathway exhibits extensive crosstalk with VHL/HIF signaling, collectively promoting metabolic reprogramming that supports glutamine consumption for nucleotide, amino acid and glutathione synthesis (30). Importantly, Beckermann *et al* (36) revealed that CD28 costimulation drives T-cell glycolysis, highlighting

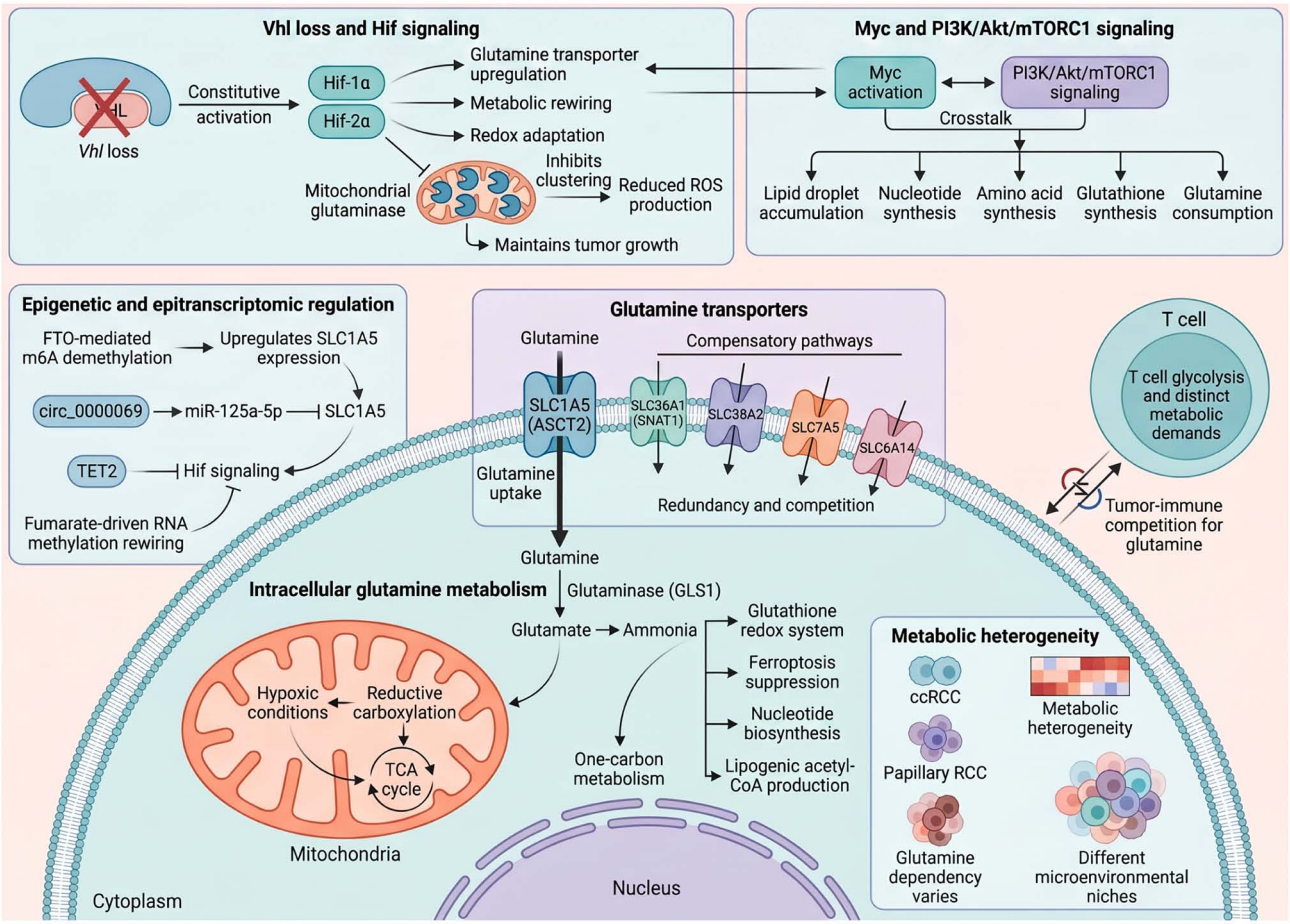


Figure 2. Molecular network regulating glutamine metabolic reprogramming in RCC. Glutamine metabolism in RCC is controlled by VHL/HIF, MYC/PI3K/AKT/mTORC1 and epigenetic/epitranscriptomic regulators (FTO, TET2). Upregulated transporters (SLC1A5) and GLS1 support tumor growth and redox adaptation. Metabolic heterogeneity and tumor-immune glutamine competition are core features. SLC1A5, solute carrier family 1 member 5; VLH, von Hippel-Lindau; HIF, hypoxia-inducible factor; mTORC1, mTOR complex 1; GLS1, glutaminase 1; miR, microRNA; TCA, tricarboxylic acid; ROS, reactive oxygen species; ccRCC, clear cell renal cell carcinoma; FTO, fat mass and obesity-associated protein; TET2, ten-eleven translocation 2.

the differential metabolic demands of immune vs. tumor cells, a theme that underscores the competitive nature of glutamine utilization in the TME.

Epigenetic modifications also play a pivotal role in regulating glutamine metabolism in RCC. Lameirinhas *et al* (37) discussed the complex interplay between metabolic reprogramming and epigenetic alterations, noting that changes in DNA methylation and histone modifications can directly affect the expression of glutamine metabolic genes. Xiao *et al* (38) identified the m^{6}A RNA demethylase fat mass and obesity-associated protein (FTO) as a HIF-independent synthetic lethal partner with VHL, demonstrating its role in regulating metabolic gene expression. Subsequently, Zhao *et al* (39) showed that FTO promotes glutamine metabolism in ccRCC through regulation of the glutamine transporter SLC1A5, establishing a direct link between RNA methylation and glutamine addiction. Zhang *et al* (40) found that TET2 suppresses VHL deficiency-driven ccRCC by inhibiting HIF signaling, indicating that the DNA demethylation machinery interacts with the central VHL/HIF axis to modulate metabolic outcomes. Additionally, Fitzsimmons *et al* (33) demonstrated that the oncometabolite fumarate rewires RNA methylation, further connecting metabolic alterations to epitranscriptomic regulation. Collectively, these findings indicate that epigenetic and epitranscriptomic mechanisms are integral to the molecular basis of glutamine metabolic reprogramming in RCC.

Glutamine transporters mediating uptake. The cellular uptake of glutamine is primarily mediated by specific amino acid transporters, whose expression is frequently upregulated in RCC. SLC1A5 serves as the predominant glutamine transporter in numerous cancers, including RCC. Kawakami *et al* (41) demonstrated that targeting SLC1A5 induces cellular senescence in ccRCC cells, confirming its functional importance. Yang *et al* (42) revealed that circ_0000069 contributes to RCC growth and glutamine metabolism by regulating microRNA (miR)-125a-5p-dependent SLC1A5 expression, illustrating the complex regulatory network controlling glutamine uptake. Furthermore, Zhao *et al* (39) established that FTO-mediated m^{6}A modification regulates SLC1A5 expression, linking epitranscriptomic regulation to glutamine transporter biology. SLC38A1 (SNAT1), another high-affinity glutamine transporter, has emerging roles in RCC, although its precise contributions require further investigation. Other transporters, including SLC38A2, SLC7A5 and SLC6A14, may also contribute to glutamine uptake, potentially providing compensatory mechanisms when primary transporters are inhibited.

Understanding the differential expression and functional redundancy of these transporters is essential for developing effective therapeutic strategies targeting glutamine import.

Intracellular glutamine metabolic pathways. Once inside the cell, glutamine feeds into multiple interconnected metabolic pathways. The initial step of glutaminolysis, namely the conversion of glutamine to glutamate and ammonia, is catalyzed by GLS1. Kaushik *et al* (7) performed *in vivo* characterization of glutamine metabolism in ccRCC using isotope tracing, identifying therapeutic targets and demonstrating that glutamine contributes to the TCA cycle primarily through reductive carboxylation under hypoxic conditions. This reductive pathway, rather than oxidative glutaminolysis, is a hallmark of ccRCC metabolism. Jiang *et al* (43) recently showed that mitochondrial uncoupling inhibits reductive carboxylation in cancer cells, suggesting that mitochondrial membrane potential is critical for this metabolic adaptation. Jo *et al* (44) used NMR-based approaches to reveal that glutamine plays alternative roles beyond simple carbon donation in kidney cancer, including supporting lipogenic acetyl-CoA production under specific conditions. The importance of glutamine for redox homeostasis is underscored by Miess *et al* (45), who demonstrated that the glutathione redox system is essential to prevent ferroptosis caused by impaired lipid metabolism in ccRCC. Furthermore, glutamine contributes to nucleotide and amino acid biosynthesis, supporting rapid proliferation. Green *et al* (46) linked methylenetetrahydrofolate dehydrogenase (NADP+ dependent) 2, methenyltetrahydrofolate cyclohydrolase, a folate cycle enzyme, to RNA methylation and metabolic reprogramming in RCC, connecting one-carbon metabolism (partly glutamine-derived) to epigenetic regulation.

Metabolic heterogeneity of glutamine utilization. RCC is not a uniform disease; substantial metabolic heterogeneity exists both between and within tumor subtypes. Krencz *et al* (47) characterized the *in situ* metabolic characteristics of papillary RCC, revealing subtype-specific metabolic adaptations that differ from ccRCC. Wu *et al* (12) comprehensively analyzed glutamine metabolism patterns in ccRCC, demonstrating associations with malignancy grade and TME composition. Single-cell and spatial metabolomics technologies have provided unprecedented insights into this heterogeneity. Jiang *et al* (48) applied single-cell and spatial transcriptomics to study mitophagy in ccRCC, revealing metabolic heterogeneity at high resolution. Similarly, Qiu *et al* (49) used single-cell RNA-sequencing to characterize metastatic RCC, showing distinct metabolic states in primary vs. metastatic lesions. Hu *et al* (50) integrated multi-dataset and machine learning analyses to investigate metabolic heterogeneity and survival outcomes in papillary RCC. These advanced approaches are critical for understanding how different tumor cell populations within the same patient may exhibit variable glutamine dependency, with profound implications for therapeutic targeting. The recognition of this heterogeneity challenges the concept of a uniform 'glutamine addiction' and instead suggests a more nuanced view where glutamine metabolism is dynamically regulated by spatial location, microenvironmental cues and treatment history.

A subtype-level comparison reveals distinct glutamine dependency patterns with therapeutic implications. In ccRCC, glutamine predominantly supports reductive carboxylation and glutathione synthesis under VHL/HIF-driven metabolic reprogramming, making GLS1 inhibition a rational but partially effective strategy due to compensatory amidotransferase activity (7). In papillary RCC, by contrast, isotope tracing demonstrates that glutamine is primarily consumed for *de novo* glutathione synthesis rather than TCA cycle anaplerosis, and papillary RCC cells exhibit a shifted oxidative phosphorylation phenotype with lower glycolytic capacity than ccRCC (47). This suggests that GLS1 inhibition may be less relevant for papillary RCC, whereas glutathione pathway targeting could be more appropriate. In chromophobe RCC, glutamine dependency appears even less prominent: These tumors exhibit marked mitochondrial accumulation and rely on endocytosis-mediated extracellular macromolecule uptake as an amino acid source, with phospholipase Cγ 2/inositol 1,4,5-trisphosphate/Ca^{2+}/protein kinase C pathway activation sustaining this process (51). Consequently, glutamine-targeted strategies are unlikely to benefit chromophobe RCC and therapies disrupting endocytic amino acid acquisition warrant investigation. Beyond papillary RCC, chromophobe RCC exhibits distinct metabolic wiring, with network-based analyses showing upregulation of glutamine anaplerosis and aspartate biosynthesis genes relative to other subtypes (51). These subtype-specific differences underscore that glutamine dependency characterized in ccRCC cannot be assumed for chromophobe or other rare RCC variants, and that therapeutic targeting of glutamine metabolism requires subtype-informed patient selection rather than a uniform approach.

4. Glutamine metabolic reprogramming remodels the immunosuppressive TME

Glutamine metabolic reprogramming in RCC fundamentally reshapes the tumor immune landscape by creating a nutrient-deprived microenvironment that suppresses anti-tumor immunity. Tumor cells outcompete immune cells for available glutamine, leading to impaired effector T-cell function while promoting immunosuppressive cell populations and checkpoint molecule upregulation (10,52). This metabolic crosstalk represents a critical mechanism of immune evasion. Fig. 3 illustrates how tumor-driven glutamine depletion impairs $CD8^+$ T cells, expands regulatory T cells (Tregs), M2-tumor-associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs), and upregulates programmed death-ligand 1 (PD-L1). Stromal metabolic crosstalk reinforces immune suppression. Targeting glutamine metabolism reverses these effects and sensitizes RCC to immune checkpoint inhibitors.

Tumor-immune cell glutamine competition. The TME of ccRCC is characterized by intense competition for limited nutrients, particularly glutamine. Tumor cells, driven by oncogenic programs such as MYC overexpression and VHL loss, exhibit an avid glutamine addiction that allows them to consume extracellular glutamine at high rates (6,8). This predatory uptake creates a state of local glutamine deprivation, directly impacting infiltrating immune cells that also

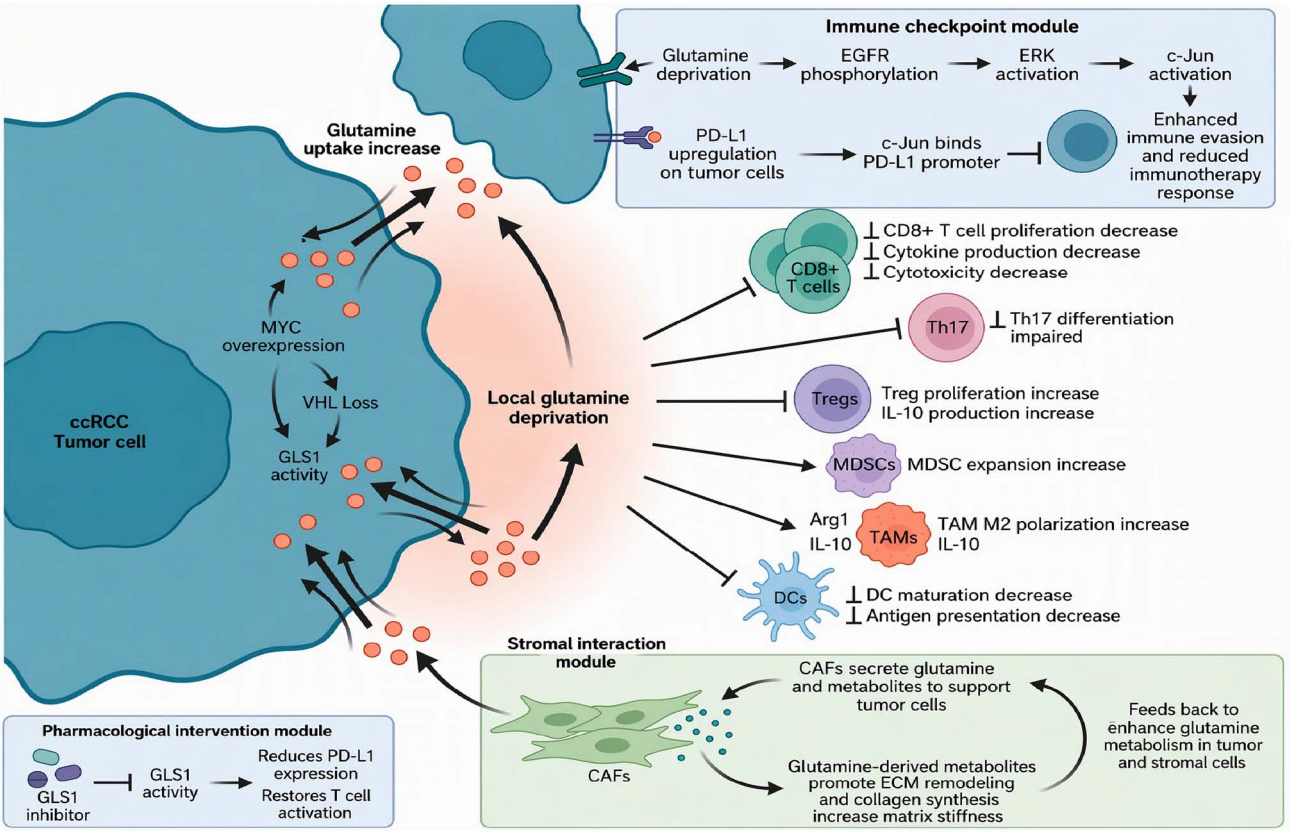


Figure 3. Glutamine metabolism remodels the immunosuppressive TME and modulates immunotherapy response in RCC. Tumor-driven glutamine depletion impairs CD8⁺ T cells, expands Tregs, M2-TAMs and MDSCs, and upregulates PD-L1. Stromal metabolic crosstalk further reinforces immune suppression. Targeting glutamine metabolism reverses immunosuppression and sensitizes RCC to immune checkpoint inhibitors. TME, tumor microenvironment; ccRCC, clear cell renal cell carcinoma; Tregs, T-regulatory cells; TAMs, tumor-associated macrophages; MDSCs, myeloid-derived suppressor cells; PD-L1, programmed cell death ligand 1; Th17, type 17 T-helper cell; DC, dendritic cell; CAF, cancer-associated fibroblast; GLS1, glutaminase 1; Arg1, arginase 1.

require this amino acid for their metabolic programs (53). Using *in vivo* isotope tracing, Reinfeld *et al* (54) demonstrated that cancer cells within the TME preferentially metabolize nutrients, including glutamine, thereby restricting availability for tumor-infiltrating lymphocytes. Consequently, effector T cells encounter a metabolically hostile environment where glutamine scarcity limits their activation and proliferation. This competitive dynamic establishes a fundamental mechanism of immune suppression that operates independently of canonical checkpoint pathways.

Glutamine metabolism regulates effector T-cell function. Effector T cells rely on glutamine as a critical fuel for clonal expansion and differentiation into functional subsets. Glutamine supports nucleotide biosynthesis, provides carbon for the TCA cycle and maintains redox balance through glutathione production (55). Under conditions of glutamine limitation, as observed in the ccRCC TME, CD8⁺ cytotoxic T lymphocytes exhibit reduced proliferation, impaired cytokine production and diminished cytotoxic capacity (56). Wei *et al* (11) systematically characterized glutamine metabolism patterns in ccRCC and found that patients with high glutamine metabolic activity displayed worse survival outcomes, which correlated with reduced infiltration of activated CD8⁺ T cells. Furthermore, glutamine deprivation selectively impacts T helper cell differentiation; Th17 cells are particularly vulnerable due to their high glutaminolytic demand, whereas Tregs may adapt through alternative metabolic pathways. Thus, tumor-driven glutamine depletion skews the T-cell repertoire toward a less effective anti-tumor response. These subset-specific vulnerabilities have been characterized primarily in non-RCC contexts; their applicability to the ccRCC TME requires direct confirmation.

Glutamine metabolism promotes immunosuppressive cell phenotypes. Beyond impairing effector cells, glutamine metabolism actively fosters the expansion and function of immunosuppressive populations. Tregs utilize glutamine to sustain their suppressive capacity, and tumor-derived glutamine deprivation paradoxically enhances Treg activity through indirect mechanisms (57,58). Fu *et al* (10) revealed that ccRCC cells consuming high levels of glutamine induce TAMs to secrete IL-23 via HIF1α activation, which in turn promotes Treg proliferation and IL-10 production, thereby suppressing cytotoxic lymphocyte function. MDSCs expand in glutamine-rich environments, and targeting glutamine metabolism has been shown to reduce MDSC accumulation and restore T-cell activity. However, direct evidence for glutamine-dependent MDSC expansion specifically in RCC is limited; much of the current understanding is extrapolated from studies in other tumor models. TAMs undergo M2 polarization when glutamine metabolism is dysregulated; glutamine-derived metabolites such as α-ketoglutarate promote the expression of M2 markers including arginase 1 and IL-10. Wu *et al* (12) demonstrated

that ccRCC tumors with high glutamine metabolism scores exhibited significantly increased infiltration of M2-polarized TAMs and MDSCs. Dendritic cells (DCs) depend on glutamine for antigen processing and presentation; glutamine scarcity impairs DC maturation and reduces their ability to prime naïve T cells. Collectively, these findings indicate that glutamine metabolic reprogramming orchestrates a multifaceted immunosuppressive network within the RCC TME.

Glutamine metabolism modulates immune checkpoint expression. Emerging evidence indicates that glutamine metabolism directly regulates the expression of immune checkpoint molecules. Ma *et al* (59) demonstrated that glutamine deprivation induces PD-L1 expression in renal cancer cells through activation of the EGFR/ERK/c-Jun signaling pathway. Mechanistically, reduced intracellular glutamine levels trigger EGFR phosphorylation, leading to downstream ERK activation and c-Jun binding to the PD-L1 promoter. This adaptive response may protect tumor cells from T cell-mediated attack under nutrient stress conditions. These seemingly divergent observations are not irreconcilable; rather, they reflect distinct experimental contexts. Acute glutamine deprivation triggers an adaptive stress response in tumor cells that transcriptionally upregulates PD-L1 via EGFR/ERK/c-Jun, potentially as a self-protective mechanism. By contrast, pharmacological GLS1 inhibition with CB-839 in preclinical RCC models downregulates PD-L1 expression and enhances T-cell activation (16), whereas GLS1 inhibition in other contexts reduces the suppressive capacity of glutamine-dependent myeloid cells and restores effector T-cell function through immune-cell-intrinsic mechanisms (60). Thus, the net immunologic effect of glutamine-targeted therapy depends on the relative contributions of tumor-cell adaptive responses and immune-cell metabolic reprogramming, which may differ by agent, dose and treatment duration. The impact of glutamine metabolism on other checkpoints such as cytotoxic T lymphocyte-associated protein 4, T-cell immunoglobulin mucin family member 3 and lymphocyte activation gene-3 remains less characterized, but transcriptomic analyses have revealed correlations between glutamine metabolic gene expression and these checkpoint molecules in ccRCC patient samples (12). Thus, targeting glutamine metabolism represents a dual strategy: It both relieves nutrient competition and reduces checkpoint-mediated immune evasion.

Glutamine metabolism and tumor-stromal cell interactions. Cancer-associated fibroblasts (CAFs) constitute a major stromal component of the RCC TME and undergo metabolic reprogramming that supports tumor progression. CAFs can secrete glutamine and other metabolites to fuel adjacent cancer cells, a phenomenon primarily demonstrated in pancreatic and prostate cancer models rather than in RCC, establishing a symbiotic metabolic crosstalk (61). The symbiotic glutamine crosstalk between CAFs and cancer cells involves a defined signaling axis. Tumor-derived palmitic acid activates TLR4/spleen-associated tyrosine kinase/NF-κB signaling in fibroblasts, inducing inflammatory CAF polarization and IL-6-dependent glutamine synthesis. CAF-derived glutamine then promotes pro-tumorigenic TAM polarization, thereby shaping an immunosuppressive myeloid landscape (61). In parallel, CAF-derived Netrin G1 (Laminet-1) interacts with netrin-G ligand-1 on cancer cells to promote glutamate and glutamine release, supporting tumor survival under nutrient stress (62). These mechanisms have been primarily demonstrated in pancreatic and prostate cancer models rather than in RCC, and direct functional validation in RCC systems is needed. Furthermore, glutamine-derived metabolites contribute to extracellular matrix (ECM) remodeling by serving as substrates for collagen synthesis and regulating matrix metalloproteinase activity, mechanisms that have been largely characterized in non-renal malignancies. Stiffened ECM, in turn, activates mechanotransduction pathways that further promote glutamine metabolism in both tumor and stromal cells, creating a positive feedback loop. The metabolic heterogeneity between primary and metastatic lesions, as well as between different RCC subtypes, adds another layer of complexity. Papillary RCC exhibits distinct glutamine utilization patterns compared to ccRCC, which may influence immune cell composition and therapeutic responses (47). Understanding these tumor-stromal metabolic interactions is essential for developing effective combination therapies that simultaneously target cancer cells and reprogram the supportive microenvironment. In summary, glutamine metabolic reprogramming in RCC remodels the immunosuppressive TME through multiple interconnected mechanisms: Competitive nutrient depletion that starves effector T cells, metabolic support for immunosuppressive cell populations, upregulation of immune checkpoints and metabolic crosstalk with stromal cells. These insights provide a strong rationale for targeting glutamine metabolism to reverse immune suppression and enhance the efficacy of immunotherapy in RCC (3,16,63).

5. Glutamine metabolism drives RCC metastasis and disease progression

Beyond its role in immune evasion, glutamine metabolic reprogramming directly fuels the metastatic cascade of RCC. Glutamine supports epithelial-mesenchymal transition (EMT), ECM remodeling, angiogenesis and cancer stem cell maintenance. These interconnected processes collectively enhance tumor cell invasion, intravasation and metastatic outgrowth (42,64,65). Understanding these mechanisms provides opportunities to target glutamine metabolism for preventing or treating metastatic RCC. The key studies dissecting how glutamine metabolism fuels RCC metastasis are summarized in Table I. Using *in vivo* models and clinical correlative analyses, these investigations have established that glutamine addiction promotes invasive behavior (8,42), supports cancer stem cell maintenance (7), facilitates ECM remodeling (64) and drives therapy-resistant angiogenesis (66). Preclinically, GLS1 inhibition or glutamine antagonism reduces metastatic burden, particularly when combined with targeted agents or immunotherapy (13,16,67).

EMT and invasion. Glutamine metabolism contributes to the acquisition of a migratory and invasive phenotype through regulation of EMT. Tumor cells with high glutamine consumption frequently display reduced E-cadherin and increased vimentin expression, accompanied by enhanced migration

Table I. Key preclinical and clinical studies investigating glutamine metabolism in RCC metastasis and disease progression.

Authors, year	Model system	Intervention	Key metabolic target	Main findings on metastasis/progression	(Refs.)
Kaushik *et al*, 2022	*In vivo* isotope tracing in ccRCC	[U-^{13}C]-glutamine tracing	Reductive carboxylation pathway	Glutamine supports lipogenesis and nucleotide synthesis essential for CSC self-renewal	(7)
Shroff *et al*, 2015	Mouse model (MYC-driven RCC)	MYC overexpression	Glutamine metabolism	MYC overexpression drives metastatic RCC through glutamine dependency	(8)
Okazaki *et al*, 2017	VHL-deficient RCC xenografts, orthotopic models	GLS1 inhibition (CB-839)	Glutaminase (GLS1)	GLS1 inhibition reduced spontaneous lung metastases in orthotopic models	(13)
Ma *et al*, 2026	ccRCC preclinical models, immune checkpoint blockade combination	Glutamine antagonist + ICIs	Glutamine metabolism	Combined with ICIs sensitizes tumors and reduces metastasis	(16)
Yang *et al*, 2023	RCC cell lines, *in vitro* assays	circ_0000069 knockdown	SLC1A5 (via miR-125a-5p)	circ_0000069 promotes migration, invasion and glutamine metabolism	(42)
Miess *et al*, 2018	ccRCC cell lines, xenografts	Glutathione system perturbation	Glutathione redox system	Glutathione system prevents ferroptosis caused by impaired lipid metabolism, enabling metastatic progression	(45)
Bezwada *et al*, 2024	Human metastatic kidney cancer specimens, *in vivo* models	Mitochondrial complex I inhibition	Mitochondrial complex I	Metastatic kidney cancers exhibit enhanced complex I activity supporting ECM invasion	(64)
Zhao *et al*, 2021	RCC cells, xenografts	QPCT targeting	QPCT (glutamine metabolism-related)	QPCT promotes sunitinib resistance by enhancing angiogenesis	(66)
Emberley *et al*, 2021	RCC xenograft models	Telaglenastat (CB-839) + cabozantinib/ everolimus	GLS1	Combination therapy reduced metastatic burden	(67)
Liu *et al*, 2015	Human ccRCC tissues (cohort study)	Correlation analysis	SLC1A5 (glutamine transporter)	High SLC1A5 expression associated with advanced stage and poor prognosis	(70)
Johnson *et al*, 2022	VHL-deficient RCC cells	STF-62247 (glutamine antagonist)	Intracellular glutamine	Decreased glutamine induces lipid droplet accumulation in VHL-deficient cells	(77)

ccRCC, clear cell renal cell carcinoma; CSC, cancer stem cell; ECM, extracellular matrix; GLS1, glutaminase 1; ICI, immune checkpoint inhibitor; QPCT, glutaminyl-peptide cyclotransferase; RCC, renal cell carcinoma; miR, microRNA; SLC1A5, solute carrier family 1 member 5, also known as ASCT2; VHL, von Hippel-Lindau.

and invasion *in vitro* (8). Shroff *et al* (8) demonstrated that MYC overexpression, which drives glutamine addiction, is sufficient to induce metastatic RCC in a mouse model, with tumors exhibiting a mesenchymal morphology and high invasive capacity. Similarly, Yang *et al* (42) showed that circ_0000069 promotes RCC cell migration and invasion by sponging miR-125a-5p, thereby derepressing the glutamine transporter SLC1A5; knockdown of this circRNA inhibited both glutamine uptake and invasive behavior. Importantly, the metabolic intermediate α-ketoglutarate, derived from glutamine via glutaminolysis, can serve as a substrate for α-ketoglutarate-dependent dioxygenases that regulate EMT transcription factors such as Snail and Twist. However, direct evidence linking α-ketoglutarate levels to specific EMT transcription factor activity in RCC remains limited. A critical contrast exists between the pro-invasive role of glutamine in most RCC models and the observation that extreme glutamine deprivation may paradoxically trigger cellular senescence (41), suggesting that a threshold level of glutamine flux is required for metastatic progression.

ECM remodeling and stromal crosstalk. Glutamine metabolism facilitates ECM remodeling, a key step for tumor cell dissemination (68). Glutamine serves as a direct precursor for collagen synthesis, and glutamine-derived glutamate fuels proline and hydroxyproline production necessary for ECM deposition (69). CAFs within the RCC stroma undergo metabolic reprogramming that supports tumor progression. To date, no published study has directly characterized glutamine metabolism or glutamine secretion by CAFs isolated from RCC; the available evidence for CAF-derived glutamine synthesis is derived exclusively from non-renal tumor models (61). In those systems, CAFs secrete glutamine and other metabolites to fuel adjacent cancer cells, establishing a symbiotic loop (64). The proposed CAF-tumor glutamine crosstalk in RCC is therefore inferred largely from studies in pancreatic and prostate cancer models, and direct functional validation in RCC systems is needed. Bezwada *et al* (64) recently reported that metastatic human kidney cancers exhibit enhanced mitochondrial complex I activity compared with primary tumors, and this metabolic shift supports ECM invasion and metastatic outgrowth. Targeting glutamine utilization may disrupt this metabolic crosstalk, but whether such inhibition preferentially affects stromal or tumor cells remains an unresolved question that warrants further investigation.

Angiogenesis and vascularization. Glutamine metabolism intersects with angiogenic signaling pathways to promote tumor vascularization. In ccRCC, VHL loss leads to constitutive HIF-2α activation, which not only drives glutamine metabolic reprogramming but also upregulates vascular endothelial growth factor (VEGF) (65). Morozumi *et al* (65) demonstrated that glutaminase inhibition reduces VEGFR2 expression and its downstream signaling by activating phosphatase and tensin homolog, thereby suppressing angiogenesis in tyrosine kinase inhibitor-resistant RCC cells. This finding is significant because it reveals a direct mechanistic link between glutamine catabolism and the VEGF pathway, suggesting that GLS1 inhibitors may exert anti-angiogenic effects independent of their direct impact on tumor cell proliferation. Conversely, certain studies have reported that moderate glutamine deprivation can upregulate VEGF secretion as a stress response, indicating a context-dependent regulation. Zhao *et al* (66) found that glutaminyl-peptide cyclotransferase (QPCT), an enzyme regulated by DNA methylation, promotes sunitinib resistance by enhancing angiogenesis in RCC, and QPCT expression correlates with glutamine metabolic gene signatures. Together, these observations indicate that glutamine metabolism supports angiogenesis through multiple mechanisms, and combining glutamine-targeting agents with anti-angiogenic therapies may yield synergistic benefits.

Cancer stem cell (CSC) properties. A subpopulation of CSCs within RCC tumors exhibits heightened glutamine dependency, which contributes to metastatic initiation and therapy resistance. CSCs rely on glutamine for maintaining redox balance through glutathione synthesis and for sustaining mitochondrial oxidative phosphorylation. Although direct evidence in RCC is still emerging, several studies have linked glutamine metabolic enzymes to stemness markers. For instance, Kaushik *et al* (7) performed *in vivo* isotope tracing and found that glutamine contributes to reductive carboxylation in ccRCC, a pathway that supports lipogenesis and nucleotide synthesis, both essential for CSC self-renewal. Furthermore, high expression of the glutamine transporter SLC1A5 is associated with poor prognosis and advanced stage (70), which may reflect enrichment of CSC-like cells. However, a critical caveat is that most studies have used bulk tumor analyses that cannot distinguish CSC-specific metabolic fluxes. Future single-cell metabolomic approaches are needed to determine whether CSCs in RCC are truly more glutamine-dependent than their differentiated progeny. Furthermore, much of the evidence linking glutamine metabolism to CSC stemness derives from pancreatic and other non-RCC cancer models, whereas direct functional evidence in RCC CSCs remains sparse (62), with only indirect associations between glutamine metabolic enzymes or transporters and stemness markers reported (7,70).

Preclinical evidence for inhibiting glutamine metabolism to block metastasis. Multiple preclinical studies have validated glutamine metabolism as a therapeutic target to prevent or reduce RCC metastasis. Okazaki *et al* (13) showed that GLS1 inhibition suppresses pyrimidine synthesis and induces oxidative stress, leading to growth arrest of VHL-deficient RCC xenografts; importantly, this treatment also reduced spontaneous lung metastases in orthotopic models. Emberley *et al* (67) reported that the GLS1 inhibitor telaglenastat (CB-839) enhanced the anti-tumor activity of cabozantinib and everolimus in RCC models, including reductions in metastatic burden. More recently, Ma *et al* (16) demonstrated that pharmacological inhibition of glutamine metabolism using a glutamine antagonist not only blocked primary tumor growth but also sensitized ccRCC tumors to immune checkpoint blockade, with a significant decrease in metastatic lesions. Despite these promising results, clinical translation has faced challenges. The phase II CANTATA trial combining telaglenastat with cabozantinib in advanced RCC did not meet its primary endpoint of progression-free survival (15), highlighting that patient selection, metabolic heterogeneity and compensatory nutrient utilization may

limit efficacy. Therefore, future strategies should focus on identifying predictive biomarkers and designing rational combination regimens that target both glutamine metabolism and metastatic drivers simultaneously.

6. Therapeutic strategies targeting glutamine metabolism in renal cell carcinoma

The dependency of RCC on glutamine for proliferation, immune evasion and metastasis has established glutamine metabolic pathways as attractive therapeutic targets (65,70-72). Multiple intervention strategies have been developed, including inhibition of glutamine transporters, blockade of key metabolic enzymes such as glutaminase and dietary glutamine restriction. Table II systematically summarizes the key preclinical and clinical studies that have evaluated these approaches.

Targeting glutamine transporters. The solute carrier family member SLC1A5 serves as the predominant glutamine transporter in ccRCC and represents a logical therapeutic entry point. Liu *et al* (70) demonstrated that high SLC1A5 expression correlates with poor prognosis in patients with ccRCC, validating its clinical relevance as a therapeutic target. Preclinical evidence supporting transporter inhibition has emerged from multiple studies. Kawakami *et al* (41) showed that pharmacological targeting of SLC1A5 induces cellular senescence in ccRCC cells, providing mechanistic insight into how transporter blockade suppresses tumor growth. The functional importance of SLC1A5 is further underscored by the finding that circ_0000069 promotes RCC progression through miR-125a-5p-dependent upregulation of this transporter, as reported by Yang *et al* (42). Despite these promising results, challenges remain, including functional redundancy among multiple glutamine transporters (SLC38A1, SLC7A5, SLC6A14) that may provide compensatory uptake when SLC1A5 is inhibited. Furthermore, most transporter-targeting agents remain in preclinical development and clinical translation has yet to be achieved.

Targeting glutaminase and downstream enzymes. GLS1, which catalyzes the first committed step of glutaminolysis converting glutamine to glutamate, has attracted substantial interest as a drug target. Okazaki *et al* (13) demonstrated that GLS1 inhibition suppresses pyrimidine synthesis and induces oxidative stress, leading to growth arrest in VHL-deficient RCC xenografts. The therapeutic potential of GLS1 inhibition was further supported by Hoerner *et al* (71), who comprehensively reviewed the rationale for targeting this enzyme in kidney cancer. The clinical candidate telaglenastat (CB-839), a selective GLS1 inhibitor, has advanced into clinical trials. In a phase I dose-escalation study, Harding *et al* (73) reported that telaglenastat was well-tolerated and demonstrated preliminary antitumor activity in patients with advanced solid tumors, including RCC. However, subsequent phase II trials yielded mixed results. The CANTATA trial, which evaluated telaglenastat plus cabozantinib vs. placebo plus cabozantinib in advanced RCC, did not meet its primary endpoint of progression-free survival, as reported by Tannir *et al* (15). Similarly, the ENTRATA trial combining telaglenastat with everolimus showed modest clinical benefit, according to Lee *et al* (14). These disappointing outcomes highlight critical limitations: Metabolic heterogeneity among patients, compensatory nutrient utilization pathways and the need for better patient selection biomarkers. A critical reappraisal of these trials reveals several factors underlying the preclinical-clinical discrepancy. First, both CANTATA and ENTRATA enrolled heavily pretreated populations: CANTATA required prior antiangiogenic therapy or nivolumab plus ipilimumab, and ENTRATA mandated at least two prior lines including a VEGFR-tyrosine kinase inhibitor (TKI), with 88% having received checkpoint inhibitors. Prior therapy exposure may select for metabolically plastic subclones that compensate through alternative anaplerotic routes. Second, GLS1 inhibition can be bypassed by asparagine synthetase-mediated asparagine production or by upregulated glycolysis and fatty acid oxidation, pathways that are not captured by baseline GLS1 expression. Third, tumor metabolic heterogeneity within individual lesions, as discussed in Section 3, means that bulk GLS1 inhibition may eliminate only a subpopulation of glutamine-dependent cells while sparing compensatory populations (14,15,74).

More recent work by Morozumi *et al* (65) demonstrated that GLS1 inhibition reduces VEGFR2 expression and suppresses angiogenesis in TKI-resistant RCC cells, suggesting that the therapeutic context may determine efficacy. In contrast to GLS1, Wang *et al* (72) found that glutamate dehydrogenase 1 (GLUD1) suppresses renal tumorigenesis by inhibiting the PI3K/Akt/mTOR pathway, indicating that not all glutamine metabolic enzymes represent viable therapeutic targets. Importantly, no study has yet demonstrated that GLS1 expression or glutamine-related gene signatures possess predictive rather than merely prognostic value for GLS1 inhibitor response. For instance, the glutamine metabolism scoring system developed by Wu *et al* (12) was constructed and validated exclusively as a prognostic tool for survival and immune microenvironment stratification in ccRCC; it has not been evaluated in any telaglenastat-treated cohort, and its predictive utility for GLS1 inhibitor response therefore remains entirely unestablished. This distinction is critical: A prognostic biomarker correlates with outcome irrespective of therapy, whereas a predictive biomarker identifies differential benefit from a specific intervention. The field currently lacks validated predictive biomarkers for glutamine-targeted therapy in RCC (75). A critical analysis of these findings suggests that targeting glutamine metabolism may be most effective in molecularly selected patient subsets rather than unselected populations.

Glutamine deprivation strategies. Limiting glutamine availability through dietary restriction or enzymatic degradation represents an alternative therapeutic paradigm. Jiménez-Alonso *et al* (76) demonstrated that artificial diets with altered amino acid levels, including glutamine restriction, induce anticancer activity in mouse models of RCC. The glutamine antagonist STF-62247 has been shown to decrease intracellular glutamine levels and induce lipid droplet accumulation specifically in VHL-deficient cells, as reported by Johnson *et al* (77). However, systemic glutamine deprivation raises significant toxicity concerns, as normal tissues, particularly the intestine and immune cells, also require

Table II. Therapeutic strategies targeting glutamine metabolism in RCC.

Authors, year	Target	Intervention	Model system	Key efficacy findings	(Refs.)
Okazaki *et al*, 2017	GLS1	CB-839; BPTES	VHL-deficient RCC xenografts; orthotopic models	GLS1 inhibition suppressed pyrimidine synthesis, induced oxidative stress, and reduced spontaneous lung metastases	(13)
Lee *et al*, 2022 (ENTRATA)	GLS1	Telaglenastat + Everolimus	Phase II trial (advanced RCC)	Modest clinical benefit; did not demonstrate significant PFS advantage	(14)
Tannir *et al*, 2022 (CANTATA)	GLS1	Telaglenastat + Cabozantinib	Phase II trial (advanced RCC)	Did not meet primary endpoint of PFS; no significant improvement over placebo + cabozantinib	(15)
Ma *et al*, 2026	Glutamine metabolism	Glutamine antagonist	ccRCC preclinical models	Blocked primary tumor growth; sensitized ccRCC to ICIs; decreased metastatic lesions	(16)
Kawakami *et al*, 2022	SLC1A5 (ASCT2)	V9302 (inhibitor); siRNA	ccRCC cell lines (A498, Caki1); xenograft	SLC1A5 inhibition suppressed tumor growth, invasion, migration; induced cellular senescence *in vitro* and *in vivo*	(41)
Emberley *et al*, 2021	GLS1	Telaglenastat (CB-839)	RCC xenograft models	Enhanced antitumor activity of cabozantinib and everolimus; reduced metastatic burden	(67)
Morozumi *et al*, 2025	GLS1	GLS1 inhibition	TKI-resistant RCC cells; xenografts	Reduced VEGFR2 expression; suppressed angiogenesis; antitumor effects in TKI-resistant cells	(65)
Hoerner *et al*, 2019	GLS1	CB-839 (telaglenastat)	Review (preclinical and clinical)	Comprehensive review establishing GLS1 inhibition as rational treatment strategy for mRCC	(71)
Harding *et al*, 2021	GLS1	Telaglenastat (CB-839)	Phase I trial (advanced solid tumors, including RCC)	Well-tolerated; preliminary antitumor activity; RP2D established (800 mg BID)	(73)
Jiménez-Alonso *et al*, 2023	Dietary amino acids	Glutamine-restricted diet	Mouse models (RCC, colon cancer, ovarian cancer)	Artificial diets with altered amino acid levels induced anticancer activity	(76)
Johnson *et al*, 2022	Glutamine	STF-62247 (antagonist)	VHL-deficient RCC cells	Decreased intracellular glutamine andglutamate; induced lipid droplet accumulation; selective toxicity to VHL-deficient cells	(77)
Gouda *et al*, 2025	GLS1	Telaglenastat + Nivolumab	Phase I/II trial (metastatic ccRCC, melanoma, NSCLC)	Well-tolerated; ORR 24% in ICI-naïve patients with ccRCC; limited efficacy in ICI-pretreated patients	(83)

ccRCC, clear cell renal cell carcinoma; GLS1, glutaminase 1; GSH, glutathione; GSSG, glutathione disulfide; ICI, immune checkpoint inhibitor; mRCC, metastatic renal cell carcinoma; NSCLC, non-small cell lung cancer; ORR, overall response rate; PD-1, programmed cell death protein 1; PET, positron emission tomography; PFS, progression-free survival; RCC, renal cell carcinoma; RP2D, recommended phase II dose; TKI, tyrosine kinase inhibitor; VHL, von Hippel-Lindau; ^{18}F-FGln, (2S,4R)-4-[^{18}F]fluoroglutamine.

glutamine for proper function. The contrasting observation by Pessino *et al* (78) that glutamine removal exerts differential effects across adenocarcinoma cell lines underscores the complexity of predicting therapeutic responses. The clinical translation of dietary glutamine restriction faces two fundamental bottlenecks. First, systemic glutamine deprivation is intrinsically toxic to normal tissues. The intestinal mucosa is particularly vulnerable: Glutamine deprivation induces apoptosis in rat intestinal epithelial cells and causes colonic epithelial damage, microvilli destruction and reduced epithelial proliferation in neonatal mice (79). Immune cells are similarly affected: Glutamine deprivation impairs $CD8^+$ T-cell function in hepatocellular carcinoma by inducing mitochondrial damage and apoptosis, reducing perforin and granzyme B production (56). Since dietary restriction cannot selectively spare these essential normal functions, it is unlikely to achieve a favorable therapeutic index when applied systemically. Second, no validated therapeutic window has been established for glutamine restriction in RCC. Preclinical studies have not defined a dose or duration that suppresses tumor glutamine flux while preserving intestinal and immune cell function, and no clinical trial has tested dietary glutamine restriction in RCC patients. Feasible optimization strategies may include tumor-selective glutamine antagonists rather than systemic dietary restriction (80,81), intermittent dosing schedules designed to allow immune cell recovery between cycles, and combination with glutaminase inhibitors at reduced doses to lower systemic exposure. However, these approaches remain preclinical and require validation in RCC models. Thus, while conceptually attractive, glutamine deprivation strategies require careful optimization to achieve therapeutic windows that preferentially affect tumor cells while sparing essential normal functions.

Combination with conventional therapies. Given the metabolic adaptability of cancer cells, combining glutamine-targeting agents with conventional therapies offers a rational strategy to overcome resistance and enhance efficacy. The rationale for such combinations has been comprehensively reviewed by van der Mijn *et al* (82), who discussed how metabolic reprogramming creates therapeutic vulnerabilities that can be exploited alongside standard treatments. Preclinically, Emberley *et al* (67) demonstrated that telaglenastat enhances the antitumor activity of the TKI cabozantinib and the mTOR inhibitor everolimus in RCC models, providing a strong rationale for clinical combination trials. Morozumi *et al* (65) further elucidated that GLS1 inhibition confers antitumor effects in TKI-resistant RCC cells by affecting VEGF signaling, suggesting that metabolic targeting may re-sensitize resistant tumors. The combination of glutamine metabolism inhibition with immune checkpoint blockade has shown particular promise. Ma *et al* (16) recently demonstrated that targeting glutamine metabolism blocks tumor growth and sensitizes ccRCC to immune checkpoint blockade, representing a paradigm-shifting approach. A phase I/II study evaluating telaglenastat plus nivolumab in RCC patients reported by Gouda *et al* (83) demonstrated manageable safety profiles and evidence of clinical activity, although larger studies are needed. Despite these encouraging results, several challenges persist, including optimal treatment sequencing, identification of predictive biomarkers and management of cumulative toxicities from combination regimens.

7. Biomarkers for predicting response to glutamine metabolism-targeted therapy in RCC

The clinical application of glutamine metabolism-targeted therapies in RCC requires reliable biomarkers to identify patients most likely to benefit from these agents. Given the metabolic heterogeneity of RCC and the complex interplay between tumor metabolism and the immune microenvironment, a single biomarker is unlikely to suffice. A multimodal approach integrating genetic, metabolic, immune and imaging biomarkers may provide the necessary precision for patient stratification (12,84). The following sections summarize current evidence regarding candidate predictive biomarkers, with critical evaluation of their clinical utility and limitations. Table III summarizes current evidence regarding candidate predictive biomarkers, with each study discussed in detail below. To avoid conceptual confusion, biomarkers in this section are classified into three categories. Prognostic biomarkers indicate disease outcome irrespective of therapy. Predictive biomarkers identify differential benefit from a specific intervention. Pharmacodynamic biomarkers reflect target engagement or pathway modulation by a drug. Most candidates discussed below were originally developed and validated as prognostic tools; their predictive utility for glutamine-targeted therapy remains largely hypothetical and requires validation in treated cohorts with appropriate control arms.

Genetic alterations. The genetic landscape of RCC directly influences glutamine dependency and may predict therapeutic response to metabolic inhibitors. VHL loss, occurring in >90% of ccRCC, represents a rational starting point, yet emerging evidence suggests that VHL status alone is insufficient as a predictive biomarker (85). Johnson and Turcotte (85) highlighted that concurrent mutations in polybromo-1, SET domain-containing protein 2 and BRCA1-associated protein 1, which constitute the 'genome protectors triad', profoundly reshape both metabolic and immune profiles in ccRCC, potentially modulating sensitivity to glutamine-targeted agents. Similarly, Zhan *et al* (4) emphasized that the complex network of gene mutations in RCC creates heterogeneous metabolic vulnerabilities that require personalized therapeutic approaches. Succinate dehydrogenase subunit B (SDHB) deficiency represents another genetic context associated with distinct metabolic derangements. Saxena *et al* (86) demonstrated that SDHB-mutant cancers exhibit impaired iron-sulfur cluster delivery, leading to pseudohypoxic signaling and metabolic reprogramming that may enhance glutamine dependence. Clinically, Lee *et al* (87) reported a case of lethal SDHB-mutated metastatic kidney cancer with persistent severe hyperlactatemia and extreme Warburg effect, suggesting that such patients might derive particular benefit from metabolic interventions. MYC amplification drives glutamine addiction in RCC, as shown by Sainero-Alcolado *et al* (34), who demonstrated that targeting MYC induces lipid droplet accumulation, indicating a metabolic shift that could be therapeutically exploited. However, to the best of our knowledge,

Table III. Candidate predictive biomarkers for glutamine metabolism-targeted therapy in RCC.

Authors, year	Biomarker category	Candidate biomarker(s)	Predictive/prognostic value	Key findings	(Refs.)
Fu *et al*, 2019	Immune	IL-23, TAMs	Prognostic; predictive only in preclinical combination models	High IL-23 expression associated with poor survival; links glutamine addiction to Treg-mediated immune evasion; IL-23 blockade augments anti-PD-1 efficacy	(10)
Wei *et al*, 2022	Metabolic + immune	PYCR1	Prognostic	PYCR1 regulates glutamine metabolism to construct immunosuppressive TME; correlates with reduced CD8+ T-cell infiltration and poor outcomes	(11)
Wu *et al*, 2024	Multi-omics (metabolic + immune)	GMRScore (6-gene signature)	Prognostic	GMRScore stratifies patients by prognosis, immune infiltration and ICI response; high GMRScore indicates immunosuppressive TME	(12)
Liu *et al*, 2015	Metabolic	SLC1A5 (ASCT2)	Prognostic	High SLC1A5 expression correlates with advanced stage, poor prognosis and aggressive ccRCC; potential biomarker for glutamine-addicted tumors	(70)
Johnson and Turcotte, 2025	Genetic	PBRM1/SETD2/ BAP1	Pathophysiologicallyplausible; not clinically validated as predictive	Concurrent mutations reshape metabolic and immune profiles; may modulate sensitivity to glutamine-targeted agents	(85)
Zhang *et al*, 2017	Metabolic	Serum amino acids	Diagnostic/prognostic	Serum glutamine and glutamate levels have predictive and prognostic value for ccRCC; correlate with tumor burden	(89)
Wang *et al*, 2025	Metabolic	Urinary amino acid profiles	Prognostic	Urinary amino acid profiles predict and assess ccRCC prognosis; non-invasive biomarker opportunity	(90)
Ozawa *et al*, 2025	Metabolic	Metabolite panel	Predictive for drug response	Metabolic landscape of ccRCC identifies metabolites predictive of drug response; metabolic heterogeneity informs patient stratification	(96)
Liu *et al*, 2026	Immune (machine learning)	Proliferating T cell-related signature	Prognostic; predictive for treatment efficacy	Machine learning-derived signature correlates with prognosis and ICI response; integrates immune-metabolic features	(97)

ccRCC, clear cell renal cell carcinoma; GMRScore, glutamine metabolism-related score; ICIs, immune checkpoint inhibitors; IL-23, interleukin-23; PD-L1, programmed death-ligand 1; PYCR1, pyrroline-5-carboxylate reductase 1; SLC1A5, solute carrier family 1 member 5 (also known as ASCT2); TAMs, tumor-associated macrophages; TME, tumor microenvironment; SETD2, SET domain-containing protein 2; BAP1, BRCA1-associated protein 1.

no prospective studies have validated these genetic alterations as predictive biomarkers for glutamine-targeted therapy. A critical limitation is that genetic mutations establish permissive metabolic states rather than deterministic dependency, and compensatory nutrient utilization pathways may circumvent pathway inhibition regardless of genotype. Evidence level for genetic biomarkers: Prognostic or pathophysiologically plausible, but not prospectively validated as predictive for any glutamine-targeted agent.

Metabolic biomarkers. Tumor expression levels of glutamine transporters and metabolic enzymes offer more direct measures of pathway dependency. Liu *et al* (70) first established that high SLC1A5 expression correlates with poor prognosis in ccRCC (prognostic evidence; no predictive validation for glutamine-targeted therapy). Wu *et al* (12) subsequently developed glutamine metabolism scoring systems that stratified patients with ccRCC into distinct metabolic subtypes with differential malignancy grades and immune microenvironment compositions (prognostic and immunophenotypic stratification; not evaluated in any telaglenastat-treated cohort). Tumors with high glutamine metabolism scores exhibited more aggressive behavior and immunosuppressive features, theoretically rendering them more susceptible to glutamine-targeted interventions. Among metabolic enzymes, Wang *et al* (72) demonstrated that GLUD1 suppresses renal tumorigenesis by inhibiting the PI3K/Akt/mTOR pathway, indicating that low GLUD1 expression might identify tumors with enhanced pathway dependency. Conversely, Fu *et al* (88) identified aldehyde dehydrogenase 18 family member A1 (ALDH18A1) as a regulator of glutamine metabolism that attenuates ccRCC progression, suggesting that high ALDH18A1 expression could serve as a favorable prognostic marker but not necessarily a predictor of therapeutic response. Circulating and urinary metabolites provide non-invasive biomarker opportunities. Zhang *et al* (89) demonstrated that serum amino acid levels, including glutamine and glutamate, have predictive and prognostic value for ccRCC. Circulating and urinary amino acid profiles currently have diagnostic and prognostic evidence in ccRCC, but no study has tested whether baseline amino acid levels predict response to GLS1 inhibition or other glutamine-targeted agents. These markers should therefore be classified as prognostic/diagnostic rather than predictive at present. Wang *et al* (90) recently validated that urinary amino acid profiles can predict and assess prognosis in ccRCC, offering a clinically accessible approach for patient monitoring. Sato *et al* (91,92) developed accurate quantification methods for urinary metabolites that manifest clinicopathological features of RCC, and separately elucidated metabolic mechanisms of sunitinib resistance using metabolomic analysis. Wettersten *et al* (5) performed combined proteomics and metabolomics analysis to reveal grade-dependent metabolic reprogramming in kidney cancer, establishing that metabolic profiles evolve with disease progression. Multiple groups have also identified distinctive urinary metabolomic signatures for RCC diagnosis, though their predictive value for therapy response remains unproven (93,94). More advanced approaches include [^{13}C]-glutamine isotope tracing to directly measure metabolic flux. Abu Aboud *et al* (6) demonstrated that glutamine addiction in kidney cancer can be exploited for real-time imaging, providing proof-of-concept for dynamic metabolic assessment. However, isotope tracing remains primarily a research tool with limited clinical applicability. A major unresolved issue is that static measurements of enzyme or transporter expression poorly reflect actual pathway flux, which is dynamically regulated by microenvironmental conditions and treatment history. Furthermore, the substantial metabolic heterogeneity within individual tumors, revealed by single-cell and spatial metabolomics, suggests that biopsy-based metabolic biomarkers may be compromised by sampling bias (95,96).

Immune biomarkers. Given that glutamine metabolism-targeted therapies are most promising in combination with immune checkpoint blockade, immune biomarkers may predict combinatorial benefit. Fu *et al* (10) demonstrated that TAMs-derived IL-23 links ccRCC glutamine addiction with immune evasion, identifying a specific immune-metabolic axis that could be targeted. Patients with high IL-23 expression or M2-polarized TAM infiltration might derive enhanced benefit from glutamine inhibition combined with ICIs. Wei *et al* (11) showed that PYCR1 regulates glutamine metabolism to construct an immunosuppressive microenvironment in ccRCC, and high PYCR1 expression correlated with reduced $CD8^+$ T-cell infiltration. This finding suggests that PYCR1 expression might identify tumors whose immunosuppression is driven by glutamine metabolism and therefore reversible by metabolic intervention. The phase I/II clinical trial of telaglenastat combined with nivolumab by Gouda *et al* (83) included correlative biomarker analyses, though definitive predictive immune signatures have not yet emerged from this study. The study incorporated correlative biomarker analyses, but no immune signature has yet demonstrated predictive value for telaglenastat plus nivolumab benefit. The immune markers discussed in this section (IL-23, PYCR1, glutamine metabolism scores) currently have prognostic associations with immunosuppressive TME features; their capacity to predict response to glutamine-targeted therapy remains unproven. Poplawski *et al* (84) demonstrated coordinated reprogramming of the renal cancer transcriptome, metabolome and secretome associated with immune tumor infiltration, suggesting that multi-omic integration may identify patients with metabolically-driven immune evasion. Machine learning approaches have been applied to identify immune-related signatures. Liu *et al* (97) developed a proliferating T cell-related signature for predicting prognosis and treatment efficacy in ccRCC, though this signature has not been specifically validated in the context of metabolic therapy. A critical caveat is that immune biomarkers are inherently dynamic, changing with treatment and disease progression. Baseline immune infiltration patterns may not predict on-treatment immune restoration, and the immunosuppressive effects of glutamine depletion could paradoxically impair anti-tumor immunity if not properly timed with ICI administration.

Imaging biomarkers. Non-invasive imaging biomarkers offer the advantage of assessing tumor metabolism in real time across all metastatic sites. Positron emission tomography (PET) imaging using glutamine analogs represents the most advanced approach. Pollard *et al* (98) developed

and validated (2S,4R)-4-[^{18}F] fluoroglutamine for PET/MR imaging of a lung metastasis model of ccRCC, demonstrating its ability to detect glutamine-avid lesions. This technique could potentially identify tumors with high glutamine uptake that are most likely to respond to glutamine-targeted therapy, though clinical validation in patients is pending. Magnetic resonance spectroscopy (MRS) provides another modality for metabolic profiling. Huynh *et al* (95) characterized the metabolomic profile of RCC using high-resolution magic angle spinning proton MRS, identifying spectral patterns associated with tumor grade and subtype. While MRS can detect glutamine and glutamate levels, its spatial resolution and sensitivity remain limited for routine clinical application. Multiparametric MRI approaches, including those integrating imaging features with transcriptomic data, have been explored. Liang *et al* (99) used renal enhanced CT images combined with bulk and single-cell RNA sequencing to reveal the tandem mechanism between tumor cells and immunocytes, suggesting that imaging features might correlate with underlying metabolic and immune states. However, existing imaging biomarkers primarily measure steady-state metabolite levels rather than pathway flux (6,98), and none have been prospectively validated as predictive biomarkers for glutamine-targeted therapy response. The high cost and limited availability of specialized imaging techniques further restrict their widespread clinical implementation (5).

In summary, while multiple candidate biomarkers have been identified across genetic, metabolic, immune and imaging domains, none have yet reached clinical validation for predicting response to glutamine metabolism-targeted therapy in RCC. The substantial metabolic heterogeneity of RCC, the dynamic plasticity of glutamine utilization pathways and the complex interplay between tumor and immune cell metabolism collectively argue that a single biomarker will be insufficient. Future efforts should focus on prospective validation of multi-parametric biomarker panels, integration of dynamic functional imaging with molecular profiling and incorporation of biomarker-driven stratification into clinical trial designs.

8. Future perspectives

Despite the growing recognition of glutamine metabolic reprogramming as a critical driver of immune evasion and immunotherapy resistance in RCC, several fundamental challenges must be addressed to translate these insights into meaningful clinical advances. A major obstacle lies in the substantial metabolic heterogeneity within and between RCC tumors, which complicates the development of uniformly effective therapeutic strategies. Zhan *et al* (4) comprehensively reviewed the core metabolic pathways in ccRCC and emphasized that individual tumors exhibit distinct metabolic vulnerabilities depending on their genetic background and microenvironmental context. Similarly, Jena and Mishra (100) recently applied multi-omics approaches to characterize tumor grade progression in ccRCC, revealing that metabolic rewiring evolves dynamically during disease progression and varies considerably among patients. These findings collectively argue against a one-size-fits-all approach and instead support the necessity of personalized metabolic intervention strategies.

The complexity of metabolic crosstalk within the TME represents another significant hurdle. Tumor cells, immune infiltrates and stromal components engage in intricate metabolic interactions that are only beginning to be understood. Poplawski *et al* (84) demonstrated coordinated reprogramming of the renal cancer transcriptome, metabolome and secretome that associates with immune tumor infiltration, highlighting how malignant cells actively reshape their environment to suppress anti-tumor immunity. Adding another layer of complexity, Zhao *et al* (9) elucidated that HIF2α inhibits glutaminase clustering in mitochondria to sustain ccRCC growth, a finding that challenges the conventional view that HIFs simply promote glutaminolysis and suggests that context-dependent metabolic regulation must be carefully considered when designing therapeutic interventions. Furthermore, Jo *et al* (44) used advanced NMR-based approaches to reveal that glutamine plays alternative roles beyond carbon donation in kidney cancer, including supporting lipogenic acetyl-CoA production under specific conditions, indicating that simply blocking glutamine entry into the TCA cycle may be insufficient for durable therapeutic effects. A critical analysis of these studies suggests that successful future therapies will likely need to target multiple nodes of glutamine metabolism simultaneously or combine glutamine-directed agents with complementary pathway inhibitors.

The emergence of resistance to glutamine metabolism-targeted therapy poses a further challenge that has become increasingly apparent from recent clinical trials. The phase II CANTATA trial combining the glutaminase inhibitor telaglenastat with cabozantinib failed to meet its primary endpoint, underscoring that metabolic plasticity allows cancer cells to adapt and circumvent single-agent metabolic blockade. Morozumi *et al* (101) systematically investigated TKI resistance in RCC cells from the perspective of glutamine metabolism and found that resistant cells rewire their metabolic networks to sustain proliferation despite glutaminase inhibition. In subsequent work, the same group demonstrated that glutaminase inhibition confers antitumor effects in TKI-resistant cells by affecting VEGF signaling, suggesting that the therapeutic context and prior treatment history profoundly influence metabolic dependencies (65). Wang *et al* (102) further identified GFPT2 as a driver of sunitinib resistance in RCC that operates through both enzyme-dependent and enzyme-independent mechanisms, illustrating the complexity of resistance pathways that converge on glutamine metabolism. Furthermore, Tian *et al* (103) revealed that hsa_circ_0072732 enhances sunitinib resistance by inhibiting ferroptosis, connecting glutamine metabolism to non-apoptotic cell death pathways that may represent alternative vulnerabilities. A critical insight emerging from these studies is that resistance mechanisms are multifactorial and frequently involve compensatory upregulation of alternative nutrient utilization pathways, suggesting that future therapeutic regimens should be designed as multi-pronged attacks rather than sequential single-agent interventions.

The development of reliable predictive biomarkers remains an urgent priority for advancing the field. Liu *et al* (97) recently employed machine learning approaches to derive a proliferating T cell-related signature for predicting prognosis and treatment efficacy in ccRCC, demonstrating the potential of computational methods to identify clinically actionable patterns. Ozawa *et al* (96) characterized the metabolic

landscape of ccRCC and searched for metabolites predictive of drug response, identifying several candidate biomarkers that warrant prospective validation. However, a critical limitation of these studies is that most are retrospective and lack prospective validation in independent patient cohorts. Future efforts must prioritize the development of validated, clinically accessible biomarker panels that integrate genetic, metabolic and immune parameters to guide patient selection for glutamine-targeted therapies.

Technological advances offer promising avenues to address these challenges. Single-cell and spatial transcriptomics approaches have begun to resolve metabolic heterogeneity at unprecedented resolution. Abdullah *et al* (104) recently applied long-read spatial transcriptomics to patient-derived ccRCC organoids, identifying heterogeneity and transcriptional remodeling following drug treatment. Liang *et al* (99) demonstrated that renal enhanced CT images can reveal tandem mechanisms between tumor cells and immunocytes based on bulk and single-cell RNA sequencing, suggesting that imaging features may eventually serve as non-invasive surrogates for underlying metabolic states. The integration of artificial intelligence and machine learning with multi-omic datasets holds particular promise for identifying novel therapeutic targets and predicting individual patient responses. Xie *et al* (105) comprehensively reviewed the molecular code of kidney cancer, outlining a path from gene mutation discovery to precision therapy that will likely incorporate metabolic targeting as a key component. Looking forward, it is conceivable that future treatment algorithms will combine ICIs with glutamine metabolism-targeting agents in carefully timed sequences, guided by real-time metabolic imaging and dynamically updated biomarker assessments, to achieve durable responses in patients with advanced RCC.

9. Conclusions

Glutamine metabolic reprogramming in ccRCC functions as a central organizer of immune evasion. Three advances emerge: HIF2α establishes a 'controlled glutamine addiction' that sustains tumor growth while avoiding deprivation-induced death; glutamine depletion remodels the TME through TAM-derived IL-23/Treg and PD-L1 axes; and GLS1 inhibition shows reproducible preclinical but limited clinical efficacy. Two contradictions persist: The preclinical-clinical efficacy gap, partly explained by persistent amidotransferase activity during GLS1 blockade, and the absence of validated predictive biomarkers. Future translation requires subtype-informed patient selection, rationally timed metabolic-immunotherapy combinations and biomarker-driven trial design.

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Authors' contributions

YL and WL conceived the review, performed the literature search and data synthesis, and drafted the manuscript. LZ and YW contributed to literature screening and critical revision of the manuscript for important intellectual content. KC and YY provided conceptual oversight, supervised the overall development of the work and revised the manuscript critcally for intellectual content. Data authentication is not applicable. All authors read and approved the final version of the manuscript and agree to be accountable for all aspects of the work, ensuring its accuracy and integrity.

Ethics approval and consent to participate

Not applicable.

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Competing interests

The authors declare that they have no competing interests.

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