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Metabolic Reprogramming in Kidney Cancer: Implications for Therapy

Elena Tena Edo[1]

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Abstract

Kidney cancer, particularly clear cell renal cell carcinoma (ccRCC), has emerged as a paradigm for cancer metabolic reprogramming, exhibiting distinctive alterations that drive tumor progression and therapeutic resistance. This comprehensive review synthesizes current knowledge of the molecular mechanisms underlying metabolic dysregulation in kidney cancer, with emphasis on the central role of VHL/HIF pathway activation and its downstream consequences on glycolysis, lipid metabolism, and glutamine utilization. We systematically analyze how pseudohypoxia-driven metabolic rewiring not only supports tumor bioenergetics and biosynthesis but also shapes an immunosuppressive microenvironment through metabolite-mediated crosstalk with stromal and immune cells. The review highlights groundbreaking therapeutic advances, including FDA-approved HIF-2α inhibitors and emerging agents targeting glycolytic enzymes, glutaminase, and lipid metabolism, while addressing the challenges of metabolic plasticity and acquired resistance. Special attention is given to innovative combination strategies that pair metabolic modulators with immunotherapy or tyrosine kinase inhibitors, supported by preclinical rationale and clinical trial data. We further discuss cutting-edge technologies transforming the field - from hyperpolarized MRI for real-time metabolic imaging to AI-driven analysis of multi-omics datasets for patient stratification. By integrating fundamental science with translational applications, this review provides a framework for understanding kidney cancer as a metabolic disease and outlines future directions for targeted therapies, biomarker development, and personalized treatment approaches. The synthesis of these insights offers both a conceptual foundation and practical guidance for researchers and clinicians working to exploit metabolic vulnerabilities in kidney cancer.

Key words kidney cancer, ccRCC, VHL, metabolic reprogramming, therapeutics

1. Faculty of Health Sciences, International University of La Rioja, Av. de la Paz, 137, 26006 Logrono, La Rioja, Spain.
Correspondence: Elena Tena Edo (Faculty of Health Sciences, International University of La Rioja, Av. de la Paz, 137, 26006 Logrono, La Rioja, Spain; Email: elenatenaedo@gmail.com).

Introduction

Kidney cancer represents a compelling model for investigating the fundamental principles of cancer metabolism, with ccRCC exhibiting some of the most profound metabolic alterations observed in human malignancies [1]. The unique metabolic phenotype of kidney cancer stems from its distinctive genetic landscape, where inactivation of the Von Hippel-Lindau (VHL) tumor suppressor gene occurs in approximately 90% of sporadic ccRCC cases [2]. This genetic alteration triggers a cascade of molecular events that fundamentally reshape cellular metabolism, creating dependencies that differ markedly from normal renal epithelium [3]. The resulting metabolic reprogramming not only supports tumor growth and proliferation but also influences disease progression, treatment resistance, and interactions with the tumor microenvironment (TME) [4, 5]. This review provides a comprehensive examination of kidney cancer metabolism, exploring its molecular foundations, pathophysiological consequences, and emerging therapeutic opportunities.

At the heart of kidney cancer's metabolic transformation lies the constitutive activation of hypoxia-inducible factors (HIFs), particularly HIF-2α, due to VHL loss [6]. Under normal oxygen conditions, VHL targets HIF-α subunits for proteasomal degradation, but in ccRCC, this regulatory mechanism fails, creating a state of pseudohypoxia regardless of actual oxygen availability [7]. HIF stabilization orchestrates a broad transcriptional program that upregulates glucose transporters (GLUT1, GLUT3) and glycolytic enzymes (HK2, PKM2, LDHA), while simultaneously suppressing mitochondrial oxidative phosphorylation [8] [9]. This metabolic shift, reminiscent of the Warburg effect but with unique kidney cancer-specific features, provides rapidly dividing tumor cells with essential biosynthetic precursors while maintaining redox homeostasis [10]. However, recent research has revealed that kidney cancer metabolism extends far beyond glycolysis, encompassing profound alterations in lipid, amino acid, and nucleotide metabolism that collectively sustain tumor growth and survival.

The lipid-rich phenotype of ccRCC represents one of its most distinctive metabolic features, visible histologically as cytoplasmic lipid droplets [11]. This characteristic results from coordinated increases in fatty acid uptake (mediated by CD36 and other transporters), enhanced de novo lipogenesis (through upregulation of FASN and ACC), and impaired lipid oxidation due to mitochondrial dysfunction [12] [13]. The metabolic implications of this lipid reprogramming are multifaceted, providing energy storage, membrane components for rapidly dividing cells, and precursors for signaling molecules that influence tumor progression. Similarly, kidney cancers develop a pronounced dependence on glutamine metabolism, utilizing this amino acid not only as a nitrogen donor for nucleotide synthesis but also as a carbon source for anaplerotic replenishment of TCA cycle intermediates [14] [15]. This metabolic flexibility enables tumors to adapt to nutrient-poor conditions and resist therapeutic interventions.

Beyond cancer cell-intrinsic metabolic changes, kidney tumors actively remodel their microenvironment through metabolic interactions that influence disease progression and treatment response [16]. The glycolytic TME becomes enriched in lactate and other metabolites that suppress immune cell function while promoting angiogenesis [17, 18]. Cancer-associated fibroblasts (CAFs) contribute to this metabolic symbiosis by providing alternative nutrient sources, while endothelial cells adapt to the hypoxic conditions by altering their own metabolic preferences [19, 20]. These complex interactions create therapeutic challenges but also reveal new vulnerabilities that could be exploited for more effective treatments.

The clinical implications of kidney cancer metabolism have become increasingly apparent with the development of targeted therapies. The recent FDA approval of belzutifan, a HIF-2α inhibitor, validates the therapeutic potential of targeting cancer metabolism, while numerous other metabolic inhibitors are in clinical development [21]. However, significant challenges remain, including metabolic heterogeneity within tumors, the development of resistance mechanisms, and the need for reliable biomarkers to guide therapy selection. Emerging technologies such as metabolomic profiling, hyperpolarized MRI, and single-cell analysis are providing unprecedented insights into kidney cancer metabolism, enabling more precise targeting of metabolic vulnerabilities [22].

Metabolic pathways dysregulated in kidney cancer

Kidney cancer, particularly ccRCC undergoes significant metabolic reprogramming due to genetic and epigenetic alterations [11, 23]. A defining characteristic is the enhanced glycolytic flux, sustained even under normoxic conditions (the Warburg effect), driven by HIFs following loss of the VHL tumor suppressor (**Figure 1**) [24].

Lipid metabolism is also profoundly altered, with increased fatty acid uptake and storage to support membrane biosynthesis and energy reserves. Glutamine metabolism is similarly reconfigured, supplying critical precursors for nucleotide synthesis and glutathione production, thereby sustaining proliferation and redox balance [25]. Additionally, mitochondrial dysfunction impairs oxidative phosphorylation, further shifting dependence toward anaerobic metabolic pathways [26]. These adaptations not only fuel tumor growth and survival but also expose metabolic vulnerabilities that could be therapeutically targeted [27]. Elucidating these dysregulated pathways is essential for designing precision therapies to disrupt cancer metabolic dependencies and improve clinical outcomes.

Glycolysis and the warburg effect in kidney cancer

A hallmark of metabolic reprogramming in kidney cancer, particularly ccRCC, is the preferential utilization of glycolysis for energy production even in the presence of oxygen - a phenomenon termed the Warburg effect [6]. This metabolic shift is driven primarily by the constitutive stabilization of HIF-1α and HIF-2α due to loss of the VHL tumor suppressor. The enhanced glycolytic flux provides rapidly proliferating tumor cells with essential biosynthetic intermediates, including nucleotides, amino acids, and lipids, while simultaneously maintaining redox homeostasis through lactate production. Importantly, the Warburg effect supports tumor growth in the typically hypoxic microenvironment of renal carcinomas by reducing oxygen dependence for ATP generation [28]. This metabolic adaptation not only facilitates energy production but also creates a microenvironment that promotes immune evasion and therapeutic resistance [29]. The molecular underpinnings of glycolytic dysregulation in kidney cancer present promising targets for therapeutic intervention, including inhibitors of key glycolytic enzymes and HIF signaling pathways [30, 31].

Lipid metabolism reprogramming in kidney cancer

Kidney cancer exhibits profound alterations in lipid metabolism that support tumor growth and survival [32]. ccRCC is the most common renal malignancy, is particularly characterized by excessive lipid accumulation, visible histologically as cytoplasmic lipid droplets [33]. This metabolic rewiring is driven by multiple mechanisms, including HIF-mediated upregulation of lipid

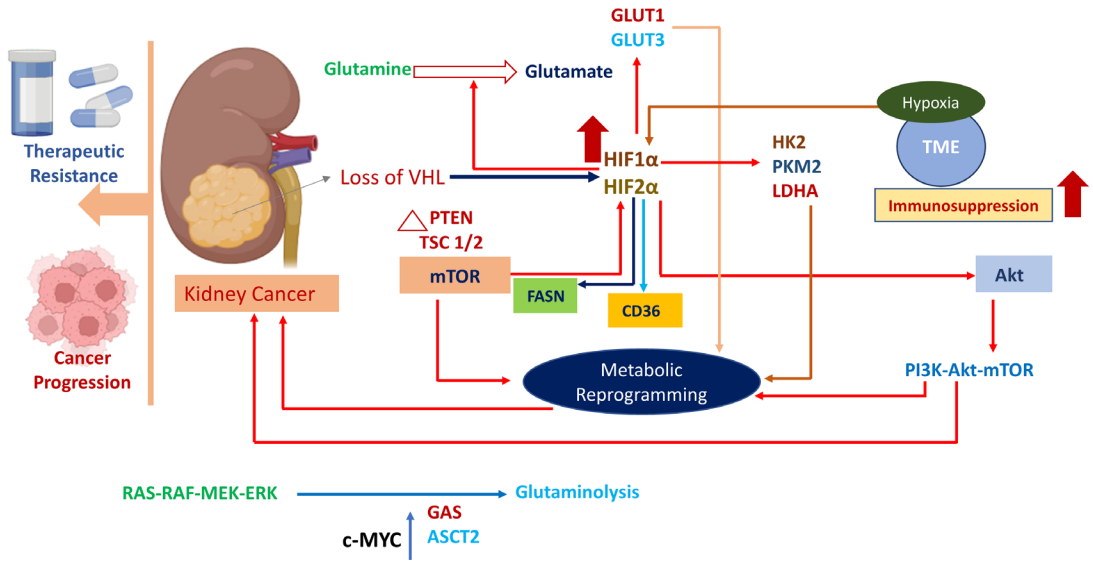

Figure 1. Metabolic reprogramming drives kidney cancer progression. Stabilization and upregulation of HIF1α and HIF2α occur because of Loss of VHL. Metabolic pathways are dysregulated and rewired by alteration of several mediators (GLUT1, GLUT3, HK2, LDHA, etc.) which are activated by the action of HIF1α and HIF2α. Hypoxia is initiated in TME leading to immunosuppression through suppression of cytotoxic T-cells.

uptake receptors (e.g., CD36), enhanced de novo lipogenesis through increased expression of fatty acid synthase (FASN) and ATP-citrate lyase (ACLY), and impaired lipid oxidation due to mitochondrial dysfunction [13]. The resulting lipid-rich environment not only provides energy stores and membrane building blocks for rapidly proliferating tumor cells but also generates signaling molecules that promote tumor progression [34]. Notably, lipid droplets serve as reservoirs for cholesterol esters and phospholipids that can be mobilized to fuel cancer cell growth under nutrient-deprived conditions [35]. Furthermore, lipid-derived metabolites function as signaling molecules that modulate oncogenic pathways and contribute to the immunosuppressive TME. These metabolic adaptations present promising therapeutic targets, with several inhibitors of lipid metabolism currently under investigation for kidney cancer treatment.

Glutamine dependency and amino acid metabolism in kidney cancer

Renal cell carcinomas, particularly clear cell subtypes, demonstrate marked glutamine addiction as part of their metabolic reprogramming. This dependence stems from the tumor's need to replenish tricarboxylic acid (TCA) cycle intermediates (anaplerosis) and generate biosynthetic precursors for nucleotides, proteins, and antioxidants [36] [37]. The frequent loss of VHL and subsequent HIF stabilization upregulate glutamine transporters (ASCT2, SN2) and key enzymes like glutaminase (GLS), which converts glutamine to glutamate [38]. This metabolic adaptation becomes crucial in kidney cancer as mitochondrial dysfunction limits glucose-derived acetyl-CoA entry into the TCA cycle [6]. Beyond energy production, glutamine metabolism supports redox balance by maintaining glutathione levels and provides nitrogen for non-essential amino acid synthesis through transamination reactions. Interestingly, kidney tumors also alter other amino acid pathways - notably upregulating serine/glycine metabolism for one-carbon units and modulating branched-chain amino acid catabolism. These interconnected amino acid fluxes create metabolic vulnerabilities, with preclinical studies showing sensitivity to glutaminase inhibitors and amino acid deprivation strategies. The emerging understanding of kidney cancer's amino acid metabolic network offers promising therapeutic avenues to target this nutrient dependency while potentially overcoming resistance to conventional therapies [31, 39].

Key drivers of metabolic reprogramming in kidney cancer

The metabolic rewiring observed in kidney cancer, specifically ccRCC is orchestrated by several interconnected molecular drivers [32]. The most prominent is the inactivation of the VHL tumor suppressor, which leads to constitutive stabilization of HIF-1α and HIF-2α [40]. These transcription factors activate a transcriptional program that upregulates glycolysis, enhances glutamine metabolism, and suppresses oxidative phosphorylation [41]. Concurrently, mutations in chromatin-modifying genes (e.g., PBRM1, SETD2) and activation of the PI3K-AKT-mTOR pathway further reshape metabolic networks by altering nutrient sensing and anabolic processes [42]. The TME, characterized by hypoxia and nutrient deprivation, exerts additional selective pressure that reinforces metabolic adaptations [43]. Importantly, these drivers converge to create a metabolic phenotype characterized by increased glucose and glutamine uptake, lipid droplet accumulation, and dependence on non-canonical nutrient utilization pathways. Understanding these key regulators provides critical insights for developing targeted therapies that disrupt

cancer-specific metabolic dependencies while sparing normal tissues (**Figure 2**).

Hypoxia-inducible factors and their role in kidney cancer pathogenesis

HIF-1α and HIF-2α serve as master regulators of metabolic adaptation in kidney cancer, with their aberrant activation representing a molecular hallmark of ccRCC [44]. The constitutive stabilization of HIF isoforms, primarily resulting from biallelic inactivation of the VHL tumor suppressor, orchestrates a comprehensive transcriptional program that drives tumor progression [45]. HIF activation mediates a pseudo-hypoxic state even under normoxic conditions, upregulating glycolytic enzymes (HK2, LDHA), glucose transporters (GLUT1/3), and angiogenic factors (VEGF) to promote anaerobic metabolism and vascularization [46]. Notably, HIF-2α demonstrates particular oncogenic specificity in ccRCC, enhancing cell proliferation through cyclin D1 regulation while suppressing oxidative phosphorylation [47]. The HIF-mediated metabolic shift also extends to glutaminolysis and lipid storage, creating a tumor-permissive microenvironment [48]. Paradoxically, while HIF-1α often exhibits tumor-suppressive properties in other cancers, both isoforms collaborate in ccRCC to establish the characteristic metabolic phenotype [49]. This unique dependency on HIF signaling presents therapeutic opportunities, with several HIF-2α-specific inhibitors now in clinical development, offering targeted approaches to disrupt the metabolic foundation of kidney cancer.

Mutations in VHL, mTOR, and other metabolic regulators in kidney cancer pathogenesis

The metabolic landscape of kidney cancer is fundamentally shaped by genetic alterations in key regulatory genes, with VHL inactivation representing the seminal event in ccRCC pathogenesis [50]. Biallelic VHL loss triggers constitutive HIF stabilization, establishing the characteristic pseudohypoxic phenotype that drives glycolytic flux and angiogenesis. Complementing this, frequent mutations in mTOR pathway components (e.g., PTEN, TSC1/2) and chromatin remodelers (PBRM1, SETD2, BAP1) create a permissive environment for metabolic reprogramming [51]. The PI3K-AKT-mTOR axis emerges as a critical co-regulator, integrating nutrient availability with biosynthetic demands through control of glycolysis, lipogenesis, and protein synthesis [52]. Notably, these genetic events exhibit functional crosstalk - VHL-deficient cells show heightened mTORC1 sensitivity to amino acids, while epigenetic modifiers influence HIF-target gene accessibility [53]. Additional metabolic regulators like FH and SDH, though less frequently mutated in ccRCC, further demonstrate how mitochondrial dysfunction can propagate oncogenic metabolic shifts [54]. This interconnected mutational architecture not only sustains tumor proliferation but also creates discrete therapeutic vulnerabilities, with current strategies targeting both HIF-dependent (e.g., belzutifan) and mTOR-driven (e.g., everolimus) metabolic pathways [55]. The convergence of these genetic alterations establishes a metabolic framework where nutrient sensing, epigenetic regulation, and oxygen response systems collectively fuel kidney cancer progression.

Oncogenic signaling pathways influencing metabolism in kidney cancer

Kidney cancer pathogenesis is driven by the interplay of multiple oncogenic signaling pathways that collectively reprogram cellular metabolism to support tumor growth and survival [56]. The PI3K-AKT-mTOR axis serves as a central metabolic rheostat, coordinating nutrient uptake and anabolic processes by upregulating glucose transporters (GLUT1/3), glycolytic enzymes (HK2, PKM2), and lipogenic factors (SREBP1, ACLY) [57, 58]. This pathway functionally intersects with HIF signaling - amplified in VHL-deficient tumors - to enhance glycolytic flux while suppressing mitochondrial oxidative phosphorylation [59]. Concurrently, RAS-RAF-MEK-ERK signaling promotes glutaminolysis through c-MYC-mediated upregulation of glutaminase (GAS) and ASCT2 transporters, sustaining TCA cycle anaplerosis [60, 61]. Notably, these pathways exhibit reciprocal regulation: mTORC1 activation stabilizes HIF-α proteins, while HIF-2α transcriptionally activates AKT, creating a feed-forward loop that amplifies metabolic reprogramming [62]. The tumor suppressor p53's frequent inactivation further exacerbates this

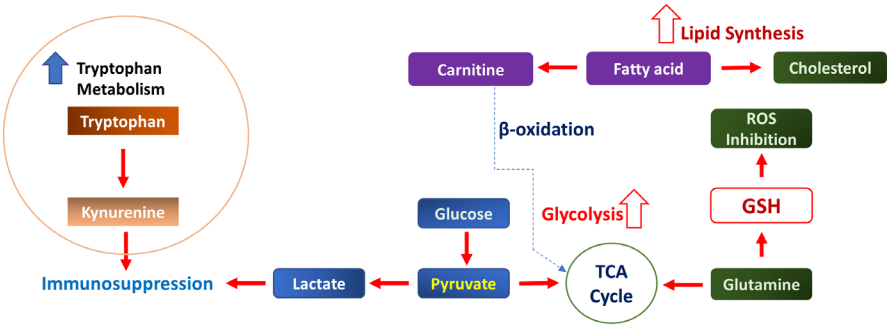

Figure 2. Metabolic reprogramming and immunosuppressive networks in kidney cancer. Enhanced glycolysis converts glucose to lactate, acidifying the TME and promoting immunosuppression. TCA cycle disruption drives oncogenic signaling in kidney cancer. Fatty acid synthesis and cholesterol accumulation sustain membrane biogenesis and signaling. Glutathione (GSH) synthesis neutralizes ROS, enabling chemoresistance.

metabolic shift by relieving repression of glycolysis and disabling oxidative metabolism checkpoints [63]. These interconnected pathways create a permissive metabolic environment characterized by heightened glucose and glutamine dependency, lipid droplet accumulation, and redox adaptation - all exploitable therapeutic vulnerabilities [64, 65]. Current targeted therapies (e.g., mTOR inhibitors, HIF-2α antagonists) and emerging metabolic approaches aim to disrupt these oncogenic signaling-metabolism nexuses in kidney cancer.

Metabolic interactions in the tumor microenvironment of kidney cancer

The kidney cancer TME represents a complex metabolic ecosystem where neoplastic cells dynamically interact with stromal components, immune cells, and vasculature through nutrient competition and metabolic crosstalk [66]. Tumor cells preferentially utilize aerobic glycolysis (Warburg effect), creating lactate-rich niches that acidify the TME and suppress antitumor immune responses by impairing cytotoxic T-cell function while promoting regulatory T-cell (Treg) activity [67, 68]. CAFs contribute to this metabolic symbiosis by secreting amino acids, lipids, and lactate that fuel tumor growth through oxidative metabolism [69]. Endothelial cells adapt to the hypoxic conditions by upregulating angiogenic factors (VEGF, PDGF) in response to HIF stabilization, further perpetuating nutrient supply to rapidly proliferating tumor cells [70]. Importantly, tumor-infiltrating myeloid cells exhibit metabolic plasticity, shifting toward arginase-mediated immunosuppression in response to hypoxia and nutrient deprivation [71, 72]. These reciprocal metabolic interactions create a self-reinforcing protumorigenic milieu that facilitates immune evasion, therapeutic resistance, and metastatic progression. Emerging therapeutic strategies targeting these metabolic networks—such as lactate dehydrogenase inhibitors, glutamine antagonists, and immune-metabolic checkpoint modulators—aim to disrupt tumor-stromal co-dependencies and restore antitumor immunity in kidney cancer.

Crosstalk between tumor cells and stroma in kidney cancer

The bidirectional metabolic interplay between tumor cells and stromal components in kidney cancer creates a dynamic microenvironment that fuels disease progression. CAFs actively secrete lactate, pyruvate, and ketone bodies that tumor cells utilize as alternative energy substrates through oxidative phosphorylation, particularly under glucose-deprived conditions [69]. Conversely, tumor cells release glutamate and other oncometabolites that activate CAFs, inducing their transformation into myofibroblasts that further remodel the extracellular matrix [73]. This metabolic symbiosis extends to endothelial cells, where HIF-driven VEGF secretion from tumor cells promotes angiogenesis, while the resulting neovasculature provides nutrients and oxygen that sustain tumor growth [74]. Adipocytes in perirenal fat deposits contribute free fatty acids that tumor cells internalize through CD36-mediated uptake, supporting membrane biosynthesis and energy storage [75]. Importantly, this crosstalk is mediated by exosomal transfer of miRNAs and metabolic enzymes that reprogram recipient cells. The resulting metabolic coupling not only enhances tumor survival under stress conditions but also creates therapeutic resistance by establishing redundant nutrient acquisition pathways. Targeting these tumor-stroma metabolic interactions – through approaches like CAF depletion, anti-angiogenic therapy, or lipid metabolism inhibition – represents a promising strategy to disrupt the tumor-supportive niche in kidney cancer.

Immune cell metabolism and immunosuppression in the kidney cancer microenvironment

The metabolic landscape of kidney cancer actively shapes antitumor immunity by imposing nutrient constraints and altering immune cell functionality within the TME. Tumor cells outcompete infiltrating lymphocytes for glucose through elevated expression of GLUT1 and hexokinase-2, forcing cytotoxic T cells into a hypofunctional state characterized by impaired glycolysis and reduced interferon-γ production [76]. Conversely, myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs) thrive in this metabolically hostile environment by preferentially utilizing fatty acid oxidation and oxidative phosphorylation, which support their immunosuppressive functions [77]. The accumulation of tumor-derived lactate and kynurenine further reinforces immunosuppression by inhibiting natural killer cell activity while promoting the polarization of tumor-associated macrophages toward an M2 phenotype. Notably, the hypoxic tumor core drives PD-L1 upregulation on both cancer cells and infiltrating myeloid cells through HIF-1α stabilization, creating an immune checkpoint-rich environment (**Figure 3**) [78]. These metabolic constraints contribute to the limited efficacy of immunotherapies in kidney cancer, prompting investigations into metabolic modulators – such as lactate dehydrogenase inhibitors and IDO1 antagonists – that may reverse immunosuppression and enhance checkpoint blockade responses [79]. Understanding these immunometabolic interactions provides critical insights for developing combination strategies that simultaneously target tumor metabolism and immune evasion mechanisms.

Angiogenesis and nutrient supply in kidney cancer progression

Kidney cancer orchestrates a robust angiogenic response to sustain its metabolic demands through complex interactions between tumor cells and the vascular microenvironment. The characteristic VHL/HIF axis activation in ccRCC drives excessive vascular endothelial growth factor (VEGF) production [53], stimulating the formation of disorganized, hyperpermeable tumor vasculature. These aberrant vessels, while providing increased nutrient and oxygen supply, create a paradoxical state of chronic hypoxia due to their structural abnormalities and inefficient perfusion. Tumor cells adapt by further upregulating HIF-dependent glycolytic enzymes and glucose transporters, establishing a self-perpetuating cycle of metabolic demand and vascular recruitment [80, 81]. The resulting vasculature not only delivers glucose and glutamine but also serves as a conduit for lipid uptake from circulating lipoproteins, supporting the lipid droplet accumulation characteristic of ccRCC. Importantly, the angiogenic switch enables metastatic dissemination by providing tumor cells access to systemic circulation while simultaneously creating an immunosuppressive microenvironment through VEGF-mediated inhibition of dendritic cell maturation [82]. This understanding has led to the clinical success of anti-angiogenic therapies, though their efficacy is often limited by the emergence of alternative nutrient acquisition strategies, including enhanced macropinocytosis and vascular co-option. Current research focuses on combining VEGF pathway inhibitors with metabolic or immunotherapeutic agents to more effectively starve tumors while preventing compensatory adaptations.

Diagnostic and prognostic implications of metabolic alterations in kidney cancer

The distinct metabolic profile of kidney cancer offers clinically valuable biomarkers for disease detection, stratification, and monitoring. The hallmark lipid and glycogen accumulation in ccRCC provides diagnostic utility, with imaging modalities like

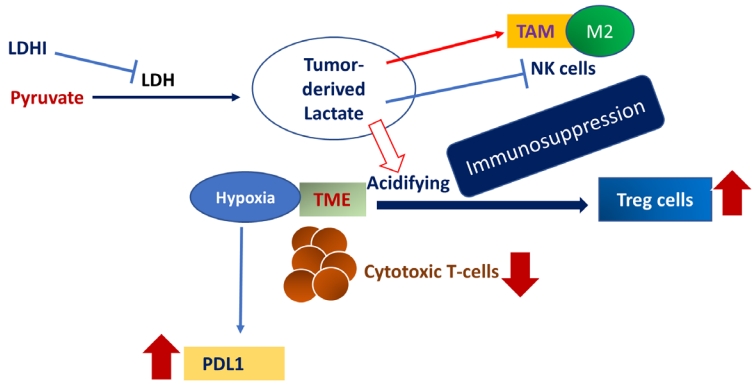

Figure 3. Immunosuppressive molecular mechanism in kidney cancer. LDH facilitates conversion of tumor-derived Lactate from pyruvate. The accumulation of LDH acidifies the TME leading to inhibition of cytotoxic T-cell functions, NK cell functions, and modulation of tumor associated macrophages (TAM). As a result, Treg cells are activated which further promotes cancer cell progression.

chemical-shift MRI effectively distinguishing malignant lesions from benign renal masses by detecting intracellular lipid content [11]. Metabolic alterations also carry prognostic significance—elevated FDG-PET avidity correlates with aggressive tumor behavior [83], while high expression of glycolytic enzymes (HK2, LDHA) and glutamine transporters (ASCT2) predicts poor survival outcomes [84]. Liquid biopsy approaches are increasingly detecting circulating tumor metabolites (succinate, 2-hydroxyglutarate) that reflect underlying mutations in IDH genes, enabling non-invasive molecular classification [85, 86]. Notably, the extent of metabolic rewiring mirrors disease progression, with metastatic lesions demonstrating amplified HIF activation and more pronounced Warburg effect compared to primary tumors. Emerging metabolic signatures, such as the ratio of ketone bodies to free fatty acids in serum, show promise for monitoring therapeutic response and detecting early recurrence. These metabolic readouts not only improve clinical decision-making but also reveal actionable targets, as tumors with specific metabolic vulnerabilities (e.g., glutamine dependency or defective oxidative phosphorylation) may show preferential sensitivity to pathway inhibitors. The integration of metabolic profiling with conventional imaging and genomic data is paving the way for precision oncology approaches in kidney cancer management.

Metabolic biomarkers in kidney cancer: current applications and emerging potential

The unique metabolic rewiring of kidney cancer has yielded clinically relevant biomarkers that enhance diagnostic precision, prognostic stratification, and therapeutic monitoring. ccRCC-specific metabolic signatures—including elevated circulating succinate levels from pseudohypoxic drive and increased urinary N-acetylaspartate reflecting altered lipid metabolism—provide non-invasive diagnostic indicators that complement imaging findings [87]. Prognostically, immunohistochemical detection of key metabolic enzymes (CAIX, GLUT1) in tumor tissues stratifies patient risk, while liquid biopsy profiles measuring kynurenine/tryptophan ratios or branched-chain amino acid patterns predict immunotherapy response [88]. Advanced imaging biomarkers, particularly 18F-FDG PET avidity and hyperpolarized 13C-pyruvate MRI, quantitatively map tumor glycolytic activity, correlating with tumor grade and metastatic potential [89]. Emerging mass spectrometry-based metabolomics now identify signature perturbations in TCA cycle intermediates (fumarate, 2-HG) that reveal underlying genetic alterations (FH/SDH mutations) and guide targeted therapy selection [90]. Notably, dynamic changes in serum acylcarnitine profiles and extracellular vesicle-derived metabolic enzymes show promise for real-time treatment monitoring. These biomarkers collectively address critical clinical challenges in kidney cancer management, from differentiating indolent from aggressive disease to detecting micro-metastases and overcoming therapeutic resistance. Their integration into multi-omics diagnostic platforms is advancing personalized management strategies that align tumor-specific metabolic vulnerabilities with precision therapies.

Imaging techniques for metabolic profiling in kidney cancer

Advanced imaging modalities now enable non-invasive metabolic profiling of kidney tumors, providing critical diagnostic and prognostic information while guiding treatment decisions. Positron emission tomography (PET) using 18F-fluorodeoxyglucose (FDG) remains the cornerstone for evaluating glycolytic activity, with standardized uptake values (SUVmax) correlating with tumor aggressiveness and metastatic potential [91, 92]. Novel PET tracers targeting other metabolic pathways—such as 11C-acetate for lipid metabolism and 18F-fluoroglutamine for amino acid uptake—are expanding the metabolic profiling capabilities [93]. Magnetic resonance spectroscopy (MRS) offers complementary data by quantifying endogenous metabolites, including elevated choline peaks reflecting membrane turnover and reduced citrate levels characteristic of ccRCC. Emerging hyperpolarized 13C-pyruvate MRI techniques dynamically track real-time conversion of pyruvate to lactate, directly visualizing Warburg effect activity with unprecedented spatial resolution [94]. Chemical shift imaging reliably detects intracellular lipid content, distinguishing clear cell from non-clear cell variants with >90% accuracy [95]. These functional imaging approaches are being integrated with radiomic analysis of conventional CT/MRI to create multiparametric metabolic signatures that predict treatment response and monitor

Table 1. Anticancer drugs effective in kidney cancer.

Name of the drug	Manufacturer	Mechanism	Reference
Lonidamine	Angelini pharma	Hexokinase-2 inhbitor	[102]
Belzutifan	Merck & Co.	Targeting HIF-2α	[103]
Telaglenastat	Calithera biosciences	Glutamine pathway inhibitor	[104]
TVB-2640	Sagimet biosciences	FASN inhibitor	[105]
FX11	Albert Einstein college of medicine	LDHA inhibitor	[106]

therapeutic efficacy. The non-invasive nature of metabolic imaging positions it as an ideal tool for serial assessment during therapy, particularly for evaluating emerging metabolism-targeted treatments like HIF-2α inhibitors and glutaminase blockers.

Therapeutic targeting of metabolic pathways in kidney cancer

The distinct metabolic dependencies of kidney cancer present promising opportunities for targeted therapeutic intervention (**Table 1**). Current strategies focus on disrupting the glycolytic flux through inhibitors of rate-limiting enzymes such as hexokinase-2 (lonidamine) or lactate dehydrogenase (FX11), which preferentially affect tumor cells exhibiting the Warburg effect [96]. The pivotal role of HIF-2α in ccRCC metabolism has been successfully targeted by belzutifan, an FDA-approved inhibitor that attenuates pseudohypoxic signaling and its downstream metabolic effects [97]. Simultaneously, glutamine pathway inhibitors like CB-839 (telaglenastat) exploit the tumor's reliance on anaplerosis by blocking glutaminase-mediated conversion to glutamate [27]. Emerging approaches target lipid metabolism through FASN inhibitors (TVB-2640) or disrupt redox balance by inhibiting NAD+ biosynthesis [98]. Notably, these metabolic therapies demonstrate synergistic potential when combined with existing anti-angiogenics or immunotherapies, as evidenced by enhanced T-cell infiltration following lactate export blockade [99]. Second-generation strategies now explore TME-specific targets, including acidosis-neutralizing agents and macrophage-directed metabolic modulators [100]. The development of pharmacodynamic biomarkers—such as hyperpolarized MRI-detected pyruvate-to-lactate conversion rates—enables real-time monitoring of metabolic drug effects, facilitating personalized treatment optimization [101]. This multifaceted approach to metabolic targeting addresses both cancer cell-intrinsic dependencies and tumor-extrinsic metabolic crosstalk, offering new avenues to overcome therapeutic resistance in kidney cancer.

Inhibitors of glycolysis and HIF signaling in kidney cancer therapeutics

The targeting of glycolytic and HIF signaling pathways represents a precision medicine approach for kidney cancer, capitalizing on the tumor's hallmark metabolic vulnerabilities. HIF-2α antagonists such as belzutifan (MK-6482) have demonstrated clinical efficacy by specifically disrupting the pseudohypoxic transcriptional program in VHL-deficient tumors, reducing expression of glycolytic enzymes (HK2, LDHA) and glucose transporters (GLUT1/3) [107]. Parallel strategies employ small molecule inhibitors of rate-limiting glycolytic components—including 2-deoxyglucose (glycolytic inhibitor) and PFK158 (PFKFB3 blocker)—to starve tumors of their preferred energy source while sparing normal cells that retain oxidative phosphorylation capacity [108]. Particularly promising are dual-action compounds that concurrently target HIF signaling and glycolysis, such as PT2385 derivatives that destabilize HIF-2α while inhibiting hexokinase activity [109]. These approaches show synergistic potential when combined with anti-angiogenic therapies, as HIF inhibition normalizes tumor vasculature while glycolytic blockade prevents metabolic adaptation. Resistance mechanisms, including upregulation of alternate HIF isoforms or activation of compensatory nutrient salvage pathways, are being addressed through next-generation inhibitors with improved target specificity and combination regimens incorporating glutaminase blockers. The development of PET-based biomarkers (18F-FDG, 18F-fluoromisonidazole) enables real-time monitoring of therapeutic response, facilitating dose optimization for these metabolism-targeted agents [110]. This therapeutic paradigm exemplifies how understanding cancer-specific metabolic dependencies can yield targeted treatments with potentially fewer off-target effects than conventional therapies.

Targeting lipid and amino acid metabolism in kidney cancer therapy

Emerging therapeutic strategies are exploiting the deregulated lipid and amino acid metabolism that underlies kidney cancer pathogenesis. The characteristic lipid droplet accumulation in clear cell RCC has prompted development of fatty acid synthase (FASN) inhibitors like TVB-2640, which disrupt de novo lipogenesis and induce tumor-specific apoptosis by depriving cancer cells of membrane precursors and signaling lipids [111]. Concurrently, inhibitors of sterol regulatory element-binding proteins (SREBP) such as fatostatin are being evaluated to block the lipogenic transcription program driven by HIF and mTOR pathways [112]. In amino acid metabolism, glutaminase inhibitors (telaglenastat) and ASCT2 blockers (V-9302) are showing promise in clinical trials by restricting tumor access to glutamine – a crucial nitrogen and carbon source for ccRCC proliferation [113]. Notably, these approaches synergize with existing therapies: lipid metabolism inhibitors enhance anti-angiogenic efficacy by reducing VEGF production, while amino acid restriction potentiates immunotherapy by alleviating immunosuppressive tryptophan/kynurenine pathways. Advanced patient stratification using lipidomic profiles and PET imaging with glutamine analogs (18F-FGln) is enabling precision targeting of these metabolic vulnerabilities. The simultaneous targeting of both lipid and amino acid pathways represents a multipronged strategy to overwhelm tumor metabolic plasticity and overcome treatment resistance in kidney cancer.

Combination therapies: metabolic drugs with immunotherapy/TKI in kidney cancer treatment

The strategic integration of metabolic modulators with immunotherapy and tyrosine kinase inhibitors (TKIs) represents a paradigm shift in kidney cancer treatment, addressing both tumor-intrinsic vulnerabilities and microenvironmental immunosuppression. Preclinical studies demonstrate that HIF-2α inhibitors (belzutifan) synergize with PD-1/PD-L1 blockade by alleviating hypoxia-driven immunosuppression while normalizing aberrant tumor vasculature when combined with VEGF-targeted TKIs [114]. Clinically, glutaminase inhibitors (telaglenastat) are being evaluated with pembrolizumab to simultaneously restrict tumor bioenergetics and enhance T-cell function by reducing myeloid-derived suppressor cell (MDSC) accumulation in the TME [115]. Similarly, lactate dehydrogenase inhibitors (GSK2837808A) are showing promise in combination regimens by reversing the lactate-mediated suppression of cytotoxic T lymphocytes while maintaining anti-angiogenic effects of TKIs [116]. Emerging trial data reveal that these combinations yield durable responses by targeting complementary resistance mechanisms—metabolic drugs prevent the glycolytic adaptation that often limits TKI efficacy, while immunotherapy counters the immunosuppressive effects of metabolic stress. Advanced biomarker strategies, including metabolic PET imaging (18F-FDG, 18F-FSPG) and immune-metabolic profiling of tumor biopsies, are enabling real-time monitoring of these synergistic effects [117]. This multidimensional therapeutic approach capitalizes on the interconnected nature of metabolic and signaling networks in kidney cancer, offering new avenues to overcome treatment resistance and improve long-term outcomes.

Challenges and future perspectives in targeting kidney cancer metabolism

Despite significant advances in understanding metabolic reprogramming in kidney cancer, several challenges hinder the clinical translation of metabolism-targeted therapies. Tumor heterogeneity and metabolic plasticity enable cancer cells to rapidly switch between energy pathways, fostering resistance to single-agent therapies that target specific metabolic nodes [118]. The dual role of certain metabolites—such as lactate functioning as both a fuel source and immunosuppressive agent—complicates therapeutic interventions [119], while systemic toxicity remains a concern when inhibiting fundamental metabolic processes shared by normal cells. Current limitations in real-time metabolic imaging and biomarker validation further impede personalized treatment strategies. Future directions include the development of multi-target inhibitors that simultaneously block compensatory pathways, along with advanced drug delivery systems like nanoparticle conjugates to enhance tumor specificity. Artificial intelligence-driven analysis of multi-omics data promises to uncover novel metabolic vulnerabilities and optimize combination regimens [120]. Clinically, the integration of metabolic modulators with immunotherapy and targeted agents in rationally designed trials—guided by robust pharmacodynamic biomarkers—will be critical. Additionally, exploring circadian regulation of cancer metabolism and host-microbiome metabolic interactions may reveal unexpected therapeutic opportunities. Overcoming these challenges requires a multidisciplinary approach that bridges basic metabolic research with innovative clinical trial designs, ultimately paving the way for more effective, durable treatments in kidney cancer.

Resistance to metabolic therapies in kidney cancer

The emergence of resistance to metabolism-targeted agents in kidney cancer stems from the remarkable metabolic plasticity and genetic adaptability of tumor cells. A primary mechanism involves compensatory upregulation of alternative nutrient acquisition pathways—for instance, tumors treated with glutaminase inhibitors frequently activate macropinocytosis to scavenge extracellular proteins or amplify ASCT2-independent glutamine transport systems [121]. Similarly, glycolytic blockade often triggers a metabolic shift toward oxidative phosphorylation through mitochondrial genome amplification or increased fatty acid β-oxidation [122]. Epigenetic remodeling enables rapid adaptation, with demethylation of metabolic gene promoters facilitating expression of bypass pathways under therapeutic pressure. The TME further contributes to resistance through metabolic symbiosis, where stromal cells supply metabolites (lactate, ketones) that rescue treated tumor cells from energy crisis. Heterogeneous expression of metabolic enzymes across tumor subclones creates inherent resistance reservoirs, while HIF stabilization in perinecrotic regions maintains tumor survival despite therapy [123]. Emerging strategies to overcome resistance include intermittent dosing to prevent adaptive responses, dual targeting of complementary metabolic nodes (e.g., concurrent glycolysis and OXPHOS inhibition), and combining metabolic drugs with epigenetic modifiers to limit transcriptional adaptation. The development of functional metabolic imaging techniques (hyperpolarized MRI, metabolic PET tracers) now enables real-time monitoring of these resistance mechanisms, guiding adaptive therapeutic strategies in clinical trials.

Emerging technologies and novel therapeutic targets in kidney cancer metabolism

Recent advances in multi-omics technologies and high-resolution metabolic imaging are uncovering novel therapeutic vulnerabilities in kidney cancer metabolism. Single-cell metabolomics has revealed previously unappreciated metabolic heterogeneity within tumors, identifying rare subpopulations with dependencies on cysteine or one-carbon metabolism that could be targeted with new small-molecule inhibitors [124]. CRISPR-based metabolic gene screening has pinpointed hexosamine biosynthesis and serine/glycine conversion as essential pathways in VHL-deficient cells, while spatial transcriptomics maps metabolic crosstalk between tumor and immune cells within the TME [125]. Emerging therapeutic targets include the mitochondrial pyruvate carrier (MPC) – inhibition of which selectively starves kidney cancer cells of TCA cycle intermediates – and the cystine/glutamate antiporter xCT, which maintains redox balance in metastatic lesions. Nanotechnology approaches are enabling targeted delivery of metabolic drugs, such as nanoparticle-encapsulated glutaminase inhibitors that preferentially accumulate in tumors. Meanwhile, AI-driven analysis of metabolic flux data is predicting patient-specific vulnerabilities by modeling individual tumor metabolic networks. These innovations are being translated clinically through innovative trial designs, including basket trials testing metabolic therapies based on molecular features rather than histology, and window-of-opportunity studies using hyperpolarized 13C-MRI to quantify real-time drug effects on tumor metabolism [101]. Together, these technological advances are expanding the arsenal of metabolism-targeted therapies while enabling precision approaches tailored to individual patient tumors.

Conclusion

The metabolic reprogramming of kidney cancer represents a fundamental hallmark of the disease, driven by genetic alterations,

microenvironmental pressures, and adaptive survival mechanisms. Key findings highlight the central role of HIF-mediated pseudohypoxia, dysregulated lipid and amino acid metabolism, and bidirectional crosstalk between tumor and stromal cells in promoting tumor progression and therapeutic resistance. While significant progress has been made in targeting these pathways—exemplified by the clinical success of HIF-2α inhibitors—challenges such as metabolic plasticity and immunosuppressive niche formation persist. Future directions will require innovative approaches, including the integration of multi-omics technologies for patient stratification, development of dual-targeting metabolic agents, and rational combinations with immunotherapy to address tumor heterogeneity. Advances in metabolic imaging and AI-driven biomarker discovery are poised to accelerate precision medicine strategies, enabling real-time monitoring of treatment efficacy. As our understanding of kidney cancer metabolism evolves, so too will opportunities to develop more effective therapies that disrupt metabolic vulnerabilities while minimizing systemic toxicity. Ultimately, translating these insights into clinical practice demands collaborative efforts between basic researchers, clinicians, and bioengineers to overcome current limitations and improve outcomes for patients with kidney cancer.

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

Author contributions

Elena Tena Edo contributed to design of the work, data collection, and drafting the article.

Competing interests

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