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Metabolic Reprogramming in Kidney Cancer

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Abstract

Kidney cancer, or renal cell carcinoma (RCC), is a disease of increasing incidence which is commonly seen in the general practice of nephrology. Despite this state of affairs, this fascinating and highly morbid disease is frequently underrepresented, or even absent, from the curriculum of nephrologists in training and is generally underemphasized in national nephrology meetings, both scientific as well as clinical. While classical concepts in cancer research in general had led to the concept that cancer is a disease resulting from mutations in the control of growth-regulating pathways, reinforced by the discovery of oncogenes, more contemporary research particularly in kidney cancer has uncovered changes in metabolic pathways mediated by those same genes which control tumor energetics and biosynthesis. This adaptation of classical biochemical pathways to the tumor's advantage has been labeled "metabolic reprogramming". For example, in the case of kidney cancer there exists near universal presence of pVHL inactivation in the most common form, clear cell RCC (ccRCC), leading to activation of hypoxia-relevant and other metabolic pathways. Studies of this and other pathways in clear cell RCC (ccRCC) have been particularly revealing, leading to the concept that ccRCC can itself be considered a "metabolic disease". For this reason, the relatively new method of metabolomics has become a useful technique in the study of ccRCC to tease out those pathways which have been reprogrammed by the tumor to its maximum survival advantage. Furthermore, identification of the "nodes" of such pathways can lead to novel areas for drug intervention in a disease for which such targets are seriously lacking. Further research and dissemination of these concepts, likely using omics techniques, will lead to clinical trials of therapeutics specifically targeted to tumour metabolism, rather than those generally toxic to all proliferating cells. Such novel agents are highly likely to be more effective than existing drugs and to have far fewer adverse effects. This review provides a general overview of the technique of metabolomics and then discusses how it and other omics techniques have been used to further our understanding of the basic biology of kidney cancer as well as identify new therapeutic approaches.

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Keywords

kidney cancer; metabolomics; therapeutics; reprogramming

Utility of metabolomics in kidney cancer

With the discovery of clonal proliferation and subsequently of oncogenes, cancer had long been considered a disease of uncontrolled cell proliferation mediated by such phenomena as constitutively activated growth factor receptors. However, long after the initially puzzling observation of enhanced glycolysis — an energetically inefficient process — occurring in aggressive tumors despite normoxia¹, a steady stream of more recent discoveries has linked cancers with a variety of metabolic changes that are only indirectly related to the more obvious phenotype of cell proliferation. Many of these metabolic derangements, especially in cancer of the kidney^{2,3}, have now been linked directly to oncogenic mutations (Table 1, permission obtained from ⁴)⁵⁻⁷. This research has led to the concept that the evolution of altered metabolism, so-called metabolic reprogramming, is associated with a kidney cancer that is most likely to thrive within the body. When evaluated critically, such reprogramming makes obvious sense because in order to enable uncontrolled proliferation of cancer cells, a tumor has basic needs for augmented levels of cellular building components, such as DNA, nucleotides, and membrane constituents, as well as high levels of molecules that regulate the enhanced tumour energetics.

With the recent advances in high-throughput technologies, the pace of parallel advances in the “omics” fields that are relevant to clinical medicine, including nephrology, has markedly accelerated. If used cautiously and with full knowledge of their inherent limitations, these techniques have the potential to alter how we diagnose and treat human diseases, and their use in nephrology, while lagging as compared to other fields, has now begun to bear fruit most notably in kidney cancer. The advent of metabolomics, in which all of the metabolites in a given tissue or biofluid are examined (with the caveat that some metabolites will be below the detection limit of the instrumentation used and others will not be readily chemically identified), is one of the latest advances in the field of omics. Although not necessarily superior to the other, older omics technologies, metabolomics does have several advantages, in that there are comparatively fewer metabolites compared with genes, transcripts and proteins, which means that there is less data to manipulate. In addition, changes in metabolites are the most accurate predictors of the signature of the actual processes that are occurring within the body, rather than changes in compounds (such as untranscribed DNA or proteins modified before or after translation) that might be superfluous to these processes⁸. In light of this advantage and the fact that metabolomics analysis can readily be performed on biofluids such as blood and urine as well as more difficultly obtained tissue, it is becoming increasingly clear that metabolomics has great potential for biomarker discovery⁹. However, serious limitations to this technique exist, mostly connected to consistency of sample collection, potential confounding effects, and limitations in detection of low-abundance or unidentifiable metabolites⁹.

Metabolomics, in its non-targeted, hypothesis-generating, and thus most useful form, is defined as the non-targeted measurement of all metabolites produced by the body. Now recognized as an “established” omics¹⁰, metabolomics has shown utility in biomarker discovery and, more successfully (at least in our hands), in the identification of new therapeutic targets and paradigms. The utility of metabolomics, perhaps more so than other established omics, lies in the fact that the metabolites measured in tissue or biofluids represent actual biochemical processes occurring in the body, such that when such processes are altered in disease states, the set of metabolites measured generated will change accordingly. This may not be the case in other omics techniques since the quantitation of genes and proteins may not correlate with their activities. Indeed, combining metabolomics with proteomics¹¹ or with transcriptomics¹² can greatly increase its utility in helping to understand RCC biology.

Metabolic reprogramming is to the cancer’s advantage

Many classical metabolic pathways are increased, decreased, or bypassed entirely in cancer cells; kidney cancer is one of the most studied, and could therefore be considered the “poster child” of malignancies characterized by metabolic reprogramming^{11,12}. For example, in addition to the well-known and continually validated Warburg effect, reductive carboxylation occurs in many clear cell renal cell carcinoma (ccRCC) cells^{13,14}. This glutamine-dependent pathway involves “backwards flow” of the tricarboxylic acid (TCA) cycle, and in addition increases an intrinsic oxidative stress buffer pathway both of which help the tumor grow in a hostile environment¹⁵. Such unexpected aberrations of metabolism in RCC have provided new opportunities for both imaging and for the development of new targets for therapeutic intervention¹⁵.

Metabolic reprogramming in ccRCC

The labelling of ccRCC as a metabolic disease arises from the fact that many metabolic pathways in this disease are reprogrammed as discussed above. The most studied gene abnormality is in *VHL*, the mutation of which results in upregulation of several key hypoxia pathways; this results in the abundant angiogenesis, as a result of vascular endothelial growth factor (VEGF), and accounts for many of the paraneoplastic effects, for example increased erythropoietin, seen in this disease. Indeed, due to these protean clinical manifestations, many endocrine related (Table 2), RCC has often been labelled the “internist’s tumor”.

Several recent studies have evaluated tumor tissues from ccRCC patients using combined metabolomic, transcriptomic, and proteomic methods. These investigations have shown expected reprogramming, such as in the glycolysis pathway (Warburg metabolism) as well as relatively unexpected, such as glutamine reprogramming into antioxidant pathways¹⁵. A summary of the reprogrammed pathways discovered from combining metabolomics and proteomics appears in Fig. 1 (Reproduced with permission from Abu About O, Weiss RH: Translating Metabolic Reprogramming into New Targets for Kidney Cancer, *Kidney Cancer, in press*). Close inspection of the altered metabolic pathways invariably leads (1) to identification of “nodes” or metabolic crossroads common to several pathways where a

given pathway branches into other pathways, or (2) to the recognition of compounds (primarily enzymes) which can be impacted by drugs or other compounds to specifically attenuate the pathway(s) of interest. Overlaid on Fig. 1 are such pathways and proposed target therapies based thereupon. The distinct advantage of targeting reprogrammed pathways is that, since they primarily occur in the tumor and not in normal tissue, they are less likely than traditional chemotherapy to result in toxic effects in normal tissue.

In addition to biomarker and therapeutic target discovery, it is possible to capitalize on cancer's altered metabolism for purposes of diagnostic as well as real-time therapeutic imaging. The current standard staging procedure for RCC employs computed tomography (CT) scanning. The high uptake of glucose by cancer cells (a signature of the Warburg effect; discussed below) can be evaluated *in vivo* using positron emission tomography (PET) imaging with the glucose analogue ^{18}F -fluorodeoxyglucose (^{18}F -FDG)¹⁶. This technique has revolutionized imaging for some malignancies¹⁷⁻¹⁹, yet is problematic in RCC due to variable tumour uptake of ^{18}F -FDG²⁰ and its secretion into the urinary system²¹, so is not commonly used for routine staging of kidney tumors.

The recent identification of glutamine reprogramming (discussed below and in reference¹¹) and the consequent requirement for this amino acid for ccRCC survival has opened up a new area of diagnostic imaging using ^{18}F -glutamine PET scanning¹⁵. While not yet evaluated in human disease, pre-clinical models show fairly convincing data that this technique will ultimately be applicable to diagnosis as well as to stratification of patients with glutamine-avid tumors and the progress of therapy with glutaminase inhibition. Given the increasing rate of advances in imaging techniques as well as radiotracers, it is likely that other reprogrammed metabolic pathways could also be exploited in this manner; this is a prime example of the clinical exploitation of metabolic reprogramming.

Metabolomic Reprogramming in RCC

The extent of reprogrammed biochemical pathways in any cancer is unlikely to ever be fully worked out, but the fact that many malignancies have common pathways⁵ has led to the investigation of those pathways in particular. In the following sections, I discuss a few aspects of metabolic reprogramming which are, at least in the current state of knowledge, most germane to ccRCC (Fig. 1).

Glycolysis

Warburg metabolism, or aerobic glycolysis, was the first historical description of metabolic reprogramming, although it is now fairly clear that Otto Warburg did not fully understand the ramifications of his discovery at the beginning of the 20th century¹. Contemporary investigations of ccRCC cells and tissues from xenografted mice and patients, using metabolomics^{22,23}, proteomics^{11,23,24}, and transcriptomics¹², have unambiguously confirmed that this phenomenon is a key component of ccRCC metabolic reprogramming. As an example of Warburg metabolism, levels of enzymes involved in glycolysis such as hexokinase-1 (HK-1), pyruvate kinase (PK-2), and lactate dehydrogenase A (LDH-A) were significantly increased in ccRCC cells and tissues²⁴. While the chemically modified glucose analog 2-deoxy-D-glucose (2-DG) acts as substrate to inhibit hexokinase²⁵, 3-

bromopyruvate (3-BrPa) is believed to interfere directly with hexokinase enzymatic activity and bind to hexokinase²⁶. In ccRCC, HIF α plays a major role in activating LDH-A, a critical enzyme in glycolysis. Recent studies targeting HIF α using PT2385 resulted in inhibition of tumor growth in the different RCC cell lines²² and now is being tested in clinical trials²⁷.

Fatty acid oxidation and lipid synthesis

Non-targeted metabolomics studies in ccRCC have demonstrated an increase in utilization of fatty acids in these cells²⁸. Consistent with this finding, inhibitors of fatty acids oxidation such as the Peroxisome proliferator-activated receptor (PPAR) α antagonist GW6471 was tested in several ccRCC models and shown to inhibit xenograft ccRCC tumor growth^{29,30}. In addition, fatty acid synthase (FASN), which is involved in building long chain fatty acids and cholesterol, was found to be overexpressed in ccRCC and associated with tumor aggressiveness and poor prognosis in this disease³¹. Inhibition of FASN by cerulin or its derivative C75 induced a rapid increase in malonyl-coA with a marked reduction in lipogenesis in multiple cancer models, including RCC cells^{32,33}.

Tryptophan

Tryptophan is an essential amino acid and is catabolized through the kynurenine pathway via the rate-limited enzyme activity of the indoleamine 2,3-dioxygenase (IDO)³⁴. Important although underreported consequences of tryptophan metabolism are (1) the formation of metabolites in the kynurenine pathway which have immunosuppressive properties³⁵, and (2) that tryptophan depletion, itself immunosuppressive, obviously follows its catabolism³⁶. In a classic example of the translational power of metabolomics, the level of tryptophan in ccRCC was shown to be reduced and the pathways of its metabolism, as analyzed by metabolomics and proteomics techniques, lead strikingly into the kynurenine pathway (Fig. 2; permission obtained from¹¹), suggesting upregulation of this pathway in this disease leading to immunosuppression¹¹. Indeed, the historical failure of IFN α therapy for human RCC is likely due to its inability to overcome the immunosuppressive environment created by increased IDO1. Consequently, inhibition of IDO prevents the purported immunosuppressive effect and enables T-cell activation in a murine immune-competent RCC model³⁷. The selective IDO inhibitor epacadostat was tested in ccRCC and found to enhance the lytic ability of tumor-antigen-specific T cells in preclinical models³⁸.

As far as translational work relevant to this paradigm, there are several ongoing clinical studies using IDO inhibitors, either singly or in combination, in refractory RCC. Two combination IDO inhibitor and checkpoint inhibitor antibody studies (clinicaltrials.gov NCT02178722, NCT02318277), a combination IDO inhibitor and JAK inhibitor study in advanced solid tumors (NCT02559492), and an IDO inhibitor alone study on refractory solid tumors (NCT02048709) are all recruiting. However, none of these studies is complete and none have utilized interferon in combination with an IDO inhibitor; however, in light of new data showing that interferon (IFN) α increases IDO levels³⁷, IFN α therapy with an IDO inhibitor should be revisited for RCC.

Glutamine

Several independent studies have shown that glutamine utilization is increased in ccRCC as compared to normal kidney tissues^{11,12,39}. Based on this data, the targeting of enzymes involved in glutamine metabolism, such as glutaminase (GLS) with the drug CB839⁴⁰, is being tested both in pre-clinical as well as clinical trials. In pre-clinical work, glutamine in ccRCC was shown to be feeding the glutathione/oxidized glutathione pathway (GSH/GSSG), an important pathway for neutralizing ROS in cells^{11,12,15}; one study even demonstrated the use of this phenomenon for real-time PET imaging of RCC which could be used not only for stratification of patients who might respond to glutaminase inhibitors, but also to be able to follow the response of these patients to such therapies¹⁵. In a clinical trial, the small molecule inhibitor of glutaminase, CB-839, either alone or in combination with the mTOR inhibitor everolimus, showed favorable results in patients with ccRCC⁴¹. Furthermore Inhibitors of NADPH synthesis such as KPT-9274 have showed decreased tumor burden in RCC mouse model⁴².

Arginine

Arginosuccinate synthase 1 (ASS1) is the rate-limiting enzyme for the conversion of citrulline to arginine for ammonia detoxification through the urea cycle in kidney⁴³. In ccRCC, ASS1 has been shown to be either not expressed or is downregulated in tumors⁴⁴, causing these cancers to be auxotrophic for arginine. This finding was confirmed in all grades of ccRCC in a recent proteomic study²⁴. Consistent with this model, arginine deprivation inhibited tumor growth in the RENCA mouse model of RCC⁴⁴. The driver of the evolution of dependence of some ccRCCs on extracellular amino acids, such as arginine, is not obvious but may also relate to enhanced synthesis of essential building blocks⁴⁵ in parallel with Warburg metabolism. The pegylated form of arginine deaminase (ADI-PEG20) can be used to deplete arginine through deamination of arginine to citrulline^{44,46}.

Summary and future directions

Despite the fact that this disease is commonly diagnosed in the renal clinic, kidney cancer has woefully been missing from the curriculum, or at best underrepresented, in many if not most nephrology training programs. However, this “internists’ tumor” is associated with fascinating changes in metabolism as compared to other cancers and has thus been aptly labelled a “metabolic disease” characterized by a high degree of “metabolic reprogramming” in multiple biochemical pathways. For these reasons, it surely merits the attention of, and study by, the intellectually-inclined nephrologist. With the advent of omics and other high throughput research techniques, kidney cancer is now recognized to be more than a disease of aberrant cell cycle progression, as was previously been considered the mechanism of all malignancies, but also critically involves reprogramming of classical metabolic pathways which are important in energy and cellular synthetic component production as well as control of immune surveillance. Thus, many aspects of diagnosis and management, from imaging to pathology to therapeutics, can capitalize on these reprogrammed pathways in ways which will lead to new insights in disease management. We foresee in the future an era in which malignancies, including RCC, will be classified on the basis of those metabolic pathways which are enhanced or otherwise altered, in addition to site of occurrence or

microscopic pathology⁴⁷. However, a word of caution is in order regarding tumor heterogeneity⁴⁸ which has shown to be especially relevant for RCC: it is likely that separate regions of the tumor have distinct reprogramming, and this will need to be worked out in the future before optimally successful treatments are developed. Based on the knowledge to date and the rapidity by which metabolic reprogramming has been translated to clinical advances, it is highly likely that additional therapies will soon be developed which target the aberrant metabolic pathways.

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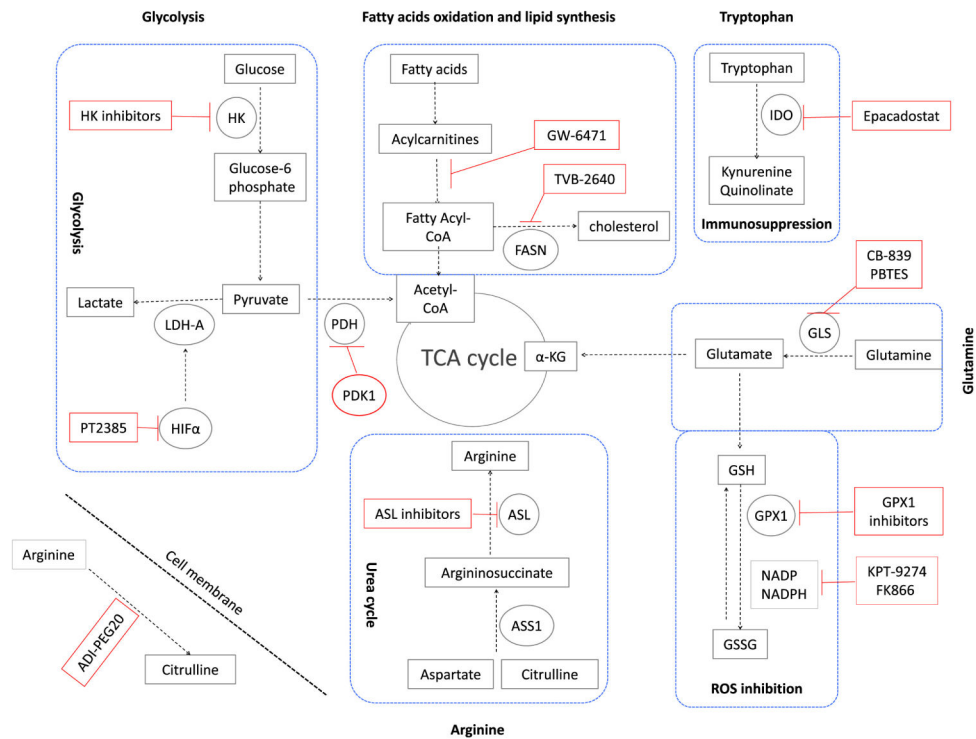


Fig. 1. Targeting metabolic reprogramming in ccRCC (from Abu About O, Weiss RH: Translating Metabolic Reprogramming into New Targets for Kidney Cancer, *Kidney Cancer, in press, with permission*)

Glycolysis can be inhibited using inhibitors for hexokinase (HK), the hypoxia-inducible factor α (HIF- α) such as PT2385, Lactate dehydrogenase (LDH-A). Glycolysis can also be inhibited by activators of pyruvate dehydrogenase kinase-1 (PDK-1), which inhibits pyruvate dehydrogenase (PDH). Fatty acid oxidation can be inhibited using peroxisome proliferator-activated receptor (PPAR α) antagonist (GW-6471). Also fatty acid synthesis can be inhibited using the fatty acid synthase (FASN) inhibitor TVB-2640. In ccRCC, upregulation of tryptophan metabolism results in increased production of the immunosuppressive metabolites kynurenine and quinolate. This pathway can be inhibited using the indoleamine 2,3-dioxygenase (IDO) inhibitor epacadostat. Glutamine metabolism can be inhibited using the glutaminase (GLS) inhibitor CB-839. α -KG is α -ketoglutarate. Glutamine is also feeding glutathione (GSH) pathway. Inhibitors of glutathione peroxidase (GPX1) and inhibitors of NADPH such as KPT-9274 and FK866 will stop changing GSH to GSSG. This reaction is responsible for scavenging reactive oxygen species (ROS) in the cell. Arginine is synthesized from citrulline in two steps of the urea cycle using the enzymes argininosuccinate synthase-1 (ASS1), and argininosuccinate lyase (ASL). As ASS1 levels are markedly decreased in all grades of ccRCC, the tumour cells are dependent on extracellular sources of arginine for their survival. Extracellular arginine can be depleted using the pegylated form of arginine deaminase enzyme (ADI-PEG20). ASL inhibitors can also be used for targeted therapy of ccRCC.

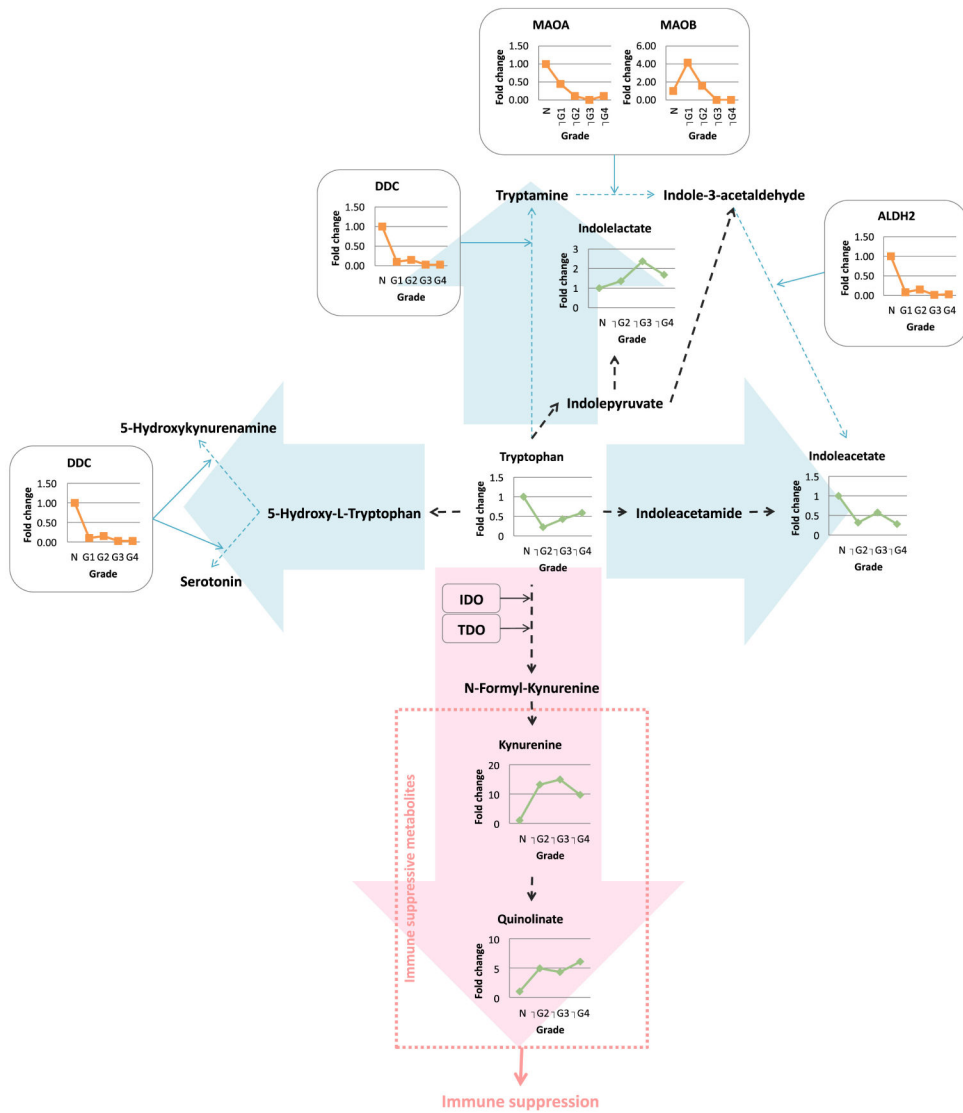


Fig. 2. Tryptophan metabolism favors a grade-dependent increase in immune suppressive metabolites (11 with permission)
 Combined proteomics and metabolomics data of human RCC tissue was overlaid onto a stylized KEGG-based pathway diagram. Green, metabolite; orange, enzyme; black dot arrow, metabolism; red arrow, upregulated pathway; blue arrow, downregulated pathway; MAO, monoamine oxidase; DDC, dopa decarboxylase; ALDH, aldehyde dehydrogenase; IDO, indoleamine 2,3-dioxygenase; TDO, tryptophan 2,3-dioxygenase

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Table 1Selected oncogenes and tumour suppressor genes that regulate metabolism⁴ (with permission)

Gene	Metabolic pathway	Relevance to RCC	Refs
<i>PTEN</i>	Inhibition of glycolysis through inactivation of Akt	2.6% of patients have biallelic loss and 16.6% of patients have monoallelic loss of <i>PTEN</i> Loss of <i>PTEN</i> is associated with high stage and grade of RCC	4950
<i>TSC1/2</i>	Deficiency leads to the Warburg effect and glutamine addiction through activation of mTOR	Mutation is a risk factor for RCC	5152
<i>AKT</i>	Upregulation of glycolysis through activation of enzymes including HK	Akt mutation is rare in RCC; activation is through PTEN loss. Akt inhibitors are being tested in clinical trials for RCC	535455,56
<i>VHL</i>	Inhibition of the Warburg effect through deactivation of HIF	Loss-of-function mutation found in >90% of patients	5758
<i>p53</i>	Downregulation of glycolysis by deactivation of GLUT1/4 and upregulation of TIGAR Upregulation of glutamine metabolism via increased transcription of GLS2	Mutation is rare in RCC	59606162
<i>LKB1</i>	Upregulation of glycolysis and β -oxidation and downregulation of lipid synthesis through activation of AMPK	Activity compromised <i>in vitro</i> , <i>in vivo</i> , and in patients	636465
<i>Myc</i>	Upregulation of the Warburg effect through activation of HK, LDHA, and PDK1 Upregulation of glutamine metabolism through GLS1 activation Upregulation of lipid synthesis through activation of FAS and SCD1	Often mutated and overexpressed in RCC Activated by HIF-2 α Overexpression induces RCC in mice	66676869 70

mTOR, mammalian target of rapamycin; HK, hexokinase; RCC, renal cell carcinoma; HIF, hypoxia-inducible factor; GLUT, glucose transporter; TIGAR, p53-inducible glycolysis and apoptosis regulator; GLS, glutaminase; APMK, AMP-activated protein kinase; LDHA, lactate dehydrogenase A; PDK1, pyruvate dehydrogenase kinase 1; FAS, fatty acid synthase; SCD1, Stearoyl-CoA desaturase 1.

Table 2

Paraneoplastic manifestations are present in up to 10–40% of patients with renal cell carcinoma

ENDOCRINE	NON-ENDOCRINE
Hypertension	Kidney failure
Polycythemia	Anemia
Hepatic dysfunction (not due to metastasis)	Coagulopathy
Hypercalcemia	Neuropathy and myopathy
Cushing's syndrome	Vasculopathy
Glucose metabolism alterations	Amyloidosis
Galactorrhea	

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