Renal cell carcinoma for the nephrologist

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Renal cell carcinoma (RCC), a malignancy whose incidence is increasing, is frequently encountered in general nephrology practice when acute and chronic kidney disease occurs in the course of disease. Importantly, when kidney disease develops in the setting of RCC, mortality is significantly increased with patients often dying of a non-cancer-related complication of kidney disease. As such, practicing nephrologists need to have a working knowledge of this cancer's biology, treatment, and complications. Nephrologists should be involved in all aspects of the care of patients with RCC including in the acute setting prior to nephrectomy and in the chronic setting for patients with post-nephrectomy chronic kidney disease and those receiving potentially nephrotoxic anti-cancer agents. This collaborative approach to RCC care will hopefully improve patient outcomes.

Kidney International (2018) ■, ■–■; https://doi.org/10.1016/j.kint.2018.01.023

KEYWORDS: acute kidney injury; chronic kidney disease; immunotherapy; nephrotoxicity; renal cell carcinoma; targeted anticancer agents; von Hippel-Lindau

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Received 15 December 2017; revised 16 January 2018; accepted 29 January 2018

Renal cell carcinoma (RCC) is commonly encountered in the practice of nephrology, particularly when acute kidney injury (AKI) or chronic kidney disease (CKD) develops in patients with RCC or when a mass is incidentally discovered during workup of kidney disease.[1,2] Importantly, RCC is a disease of increasing incidence, which is in part related to more sensitive imaging modalities.[1,2] Clear cell RCC, the focus of this review, is the most common histological subtype.[3,4] Other less common kidney cancers include papillary, chromophobe, and other rare tumors of the nephron and collecting system and are not discussed here.

Biology of clear cell renal cell carcinoma

Approximately 80% of all RCCs are of the clear cell type, in which the von Hippel-Lindau (VHL) gene product has been implicated in both the genetic and sporadic forms of RCC.[1–3] The *VHL* gene has been mapped to chromosome 3p25,[5] and its gene product, VHL protein, functions as a tumor suppressor.[6] In clear cell RCC, the *VHL* gene is commonly mutated leading to loss of function.[7–9] The presence of an inherited inactivated or deleted *VHL* allele through heterozygous inheritance is associated with a lifetime cumulative RCC incidence that approaches 70%.[10] Most sporadic RCCs are characterized by inactivation of both *VHL* alleles—one through inheritance and the other through a somatic mutation. Ultimately, this results in the loss of the regulatory VHL protein, which modifies the cellular response to hypoxia through regulation of the hypoxia-inducible factor-α (HIFα) subunit.[11]

VHL protein forms a stable complex with a number of proteins, which include cullin-2 and elongin-B and -C. The VHL complex regulates the cellular concentration of several proteins by targeting them for proteasomal degradation.[12–14] The VHL complex components act as an E3 ubiquitin ligase for target proteins, which when bound to the complex undergo proteasomal degradation. In addition to this regulatory function, VHL protein acts to regulate cytokinesis and the cell cycle, maintain primary cilium, control microtubule function, and maintain extracellular matrix integrity.

Oxygen sensing occurs within the kidney and regulates the production of erythropoietin as well as a number of other factors. Renal oxygen tension sets in motion the interaction of several factors including VHL protein, HIFα (HIF1α and 2α), the HIFαβ complex, and target *HIF* genes that ultimately determine the stimulation or suppression of a number of cellular processes. The alpha subunits are substrates for the VHL complex and are sensitive to oxygen tension. VHL

protein regulates HIFα by forming part of the E3 ubiquitin ligase complex, which degrades HIFα in the setting of normal oxygen tension.[15] HIFα degradation prevents formation of the HIFαβ complex, which binds to transcriptional gene targets at hypoxia response elements to regulate hypoxic gene expression. The prevailing oxygen tension controls post-translational prolyl hydroxylation at HIFα subunit residues and thus determines HIFα lability. With normal oxygen levels, prolyl hydroxylation leads to HIFα binding to VHL protein E3 ubiquitin ligase, resulting in degradation of the complex within the proteasome. When hypoxia is present, prolyl hyproxylase activity prevents HIFα proteolysis and permits formation of the active complex and activation of *HIF* target genes.[6,12–14] In this setting, this cascade promotes cellular proliferation, angiogenesis, and metabolic reprogramming. Some of these processes occur because production of vascular endothelial growth factor (VEGF), platelet-derived growth factor, and TGF-α are regulated by HIF1α and 2α.[6,12]

Tumor formation is thought to be related to the combined effect of various growth and angiogenic factors produced in an unregulated fashion in the setting of VHL protein deficiency. It is notable that although complete *VHL* gene inactivation occurs, its effect on clinical outcomes and disease progression are unclear. For example, tumors in those with VHL disease are often of lower grade and less likely to metastasize as compared with sporadic clear cell kidney cancers.[10,11] It is probable that other signaling pathways and cellular processes are more important in aggressive sporadic RCCs.[10,11] The malignant behavior of RCCs appears to be related to "apparent" hypoxia and dysregulation of the HIF pathway and target genes. Loss of VHL suppressor function results in the constitutive (and unregulated) stabilization of HIF independent of oxygen tension, resulting in a pseudo-hypoxic state,[16,17] which promotes abnormal biological responses and paraneoplastic syndromes.

In addition to the HIF-hypoxia pathway in clear cell RCC, a number of metabolic abnormalities are associated with the paraneoplastic syndromes observed. HIF activation due to loss of VHL protein suppressor function simulates "hypoxia" and switches cells from mitochondrial respiration to aerobic glycolysis. HIF increases glycolysis by increasing transcription of glycolytic enzymes and metabolizing pyruvate via glycolysis through increased activation of pyruvate dehydrogenase kinase-1, which blocks tricarboxylic acid cycle access to pyruvate. Down-regulation of mitochondrial oxidative phosphorylation and a reduction in tricarboxylic acid enzymes also facilitates aerobic glycolysis.[17] In addition, aerobic glycolysis, glutamine pathway reprogramming, and arginine synthetic abnormalities are also observed in clear cell RCC as a result of a deficiency of argininosuccinate synthetase-1.[18,19] Figure 1 demonstrates the various metabolic pathways associated with clear cell RCC, which supports the notion that this malignancy is not only a neoplastic process but also a "metabolic disease." These pathways offer targets for RCC therapy.

Clinical examples of the state of pseudo-hypoxia in clear cell RCC include enhanced tumor angiogenesis from increased VEGF levels and increased hemoglobin levels due to excessive erythropoietin levels. It is important to recognize that identification of this HIF-hypoxia pathway provides therapeutic targets and a rationale for targeted therapies that can blunt biochemical pathways using specific

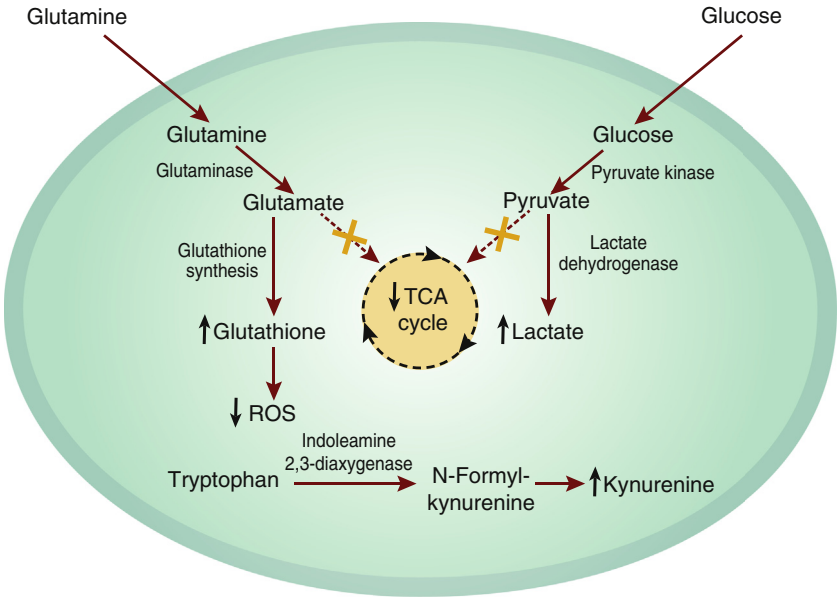

Figure 1 | Dysregulated metabolic pathways in clear cell renal cell carcinoma. Renal cancer cells increase glucose uptake, glycolysis, and lactate production, which results in decreased entry of pyruvate into the tricarboxylic acid (TCA) cycle. Cancer cells also have altered glutamine metabolism, which generates glutathione and reduces reactive oxygen species (ROS). Cancer cells also increase tryptophan metabolism, which causes increased levels of the kynurenine, an immunosuppressive metabolite. These pathways offer targets for renal cell carcinoma treatment.