The Molecular Biology of Renal Cell Carcinoma

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Renal cell carcinoma (RCC) includes a variety of disparate diseases, each of which displays interesting and novel molecular features, challenging some of the central tenets of cancer biology and lending unique insights into cancer-promoting mechanisms. The prevailing literature has focused on the most common type, the clear cell renal cell carcinoma (ccRCC) subgroup, in which familial and sporadic disease demonstrate similar molecular profiles. ccRCC is dominated by inactivating mutations in *VHL*, leading to constitutive activation of the hypoxia-inducible factors (HIFs) and resultant hypoxia response transcription signature, including changes that markedly affect cellular metabolic programs. Recent studies in ccRCC also have implicated mutations in regulators of chromatin remodeling and histone methylation. Although papillary and chromophobe histologies of RCC are highly distinct genetically, both have disruptions in metabolic signaling, suggesting that modulations of basic bioenergetics pathways may regulate kidney cell fates and phenotypes. Finally, emerging evidence of tumor heterogeneity and convergent evolution is reshaping our understanding of how these tumors evolve, underscoring which genetic events are driver mutations, and prompting further consideration of how to interpret molecular analyses of primary tumors in making assessments related to metastatic disease. The past few years have been a period of rapid discovery, which have expanded the opportunities for the renal cancer field to leverage new knowledge into developing diagnostic and therapeutic strategies.
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Approximately 65,150 Americans are anticipated to be diagnosed with cancer of the kidney and renal pelvis in 2013, and 13,680 are estimated to die from the disease.[1] Worldwide, the prevalence of disease likely exceeds 200,000. The number of affected individuals grows every year, making kidney cancer both increasingly prevalent and a clinically significant disease. Renal cell carcinoma (RCC) comprises 95% of cancers of the kidney and renal pelvis. Many cases are diagnosed at a locally confined stage (stage I–III),[2–4] but, even in the metastatic setting, nephrectomy or partial nephrectomy represents a sound first step in the management of disease. According to the Surveillance, Epidemiology and End Results (SEER) registry (2002–2008), approximately 17% of patients will present with metastatic disease; many more will suffer recurrence following surgery in earlier stages rendered with definitive intent. Although metastatic RCC is generally incurable, tyrosine kinase inhibitor therapy targeting the vascular endothelial growth factor receptor (VEGFR) serves as the mainstay of treatment.[5] Metastasectomy, careful monitoring of indolent disease, and high-dose interleukin (IL)-2 therapy remain options in carefully selected cases. Clear cell renal cell carcinoma (ccRCC) comprises the vast majority of RCCs, up to 92%.[6] Other histologic subtypes of RCC include papillary types 1 and 2, chromophobe, and other less common varieties.

Since the isolation of the von Hippel-Lindau gene (*VHL*) in 1993,[7] there has been steady progress in the discovery of new knowledge regarding RCC molecular biology, with acceleration over the last

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few years corresponding to the advent of high-throughput methods of genomic analysis. The majority of discovery-oriented research in this field has focused on ccRCC. Non–clear cell renal carcinoma has been addressed in a separate article in this issue of *Seminars in Oncology*; the molecular biology of these subtypes provides an interesting contrast to the ccRCC paradigm. Although we will touch on non–clear cell disease, and efforts to clarify the definitions of these disorders, this article will focus primarily on reviewing highlights in the molecular biology of ccRCC.

THE VHL–HIF AXIS

The roots of our knowledge regarding the genetic basis for ccRCC reach back more than 100 years. Collins reported on vascular-appearing growths involving the retina and occurring in a familial context in 1894.[8] Von Hippel and Lindau later corroborated these findings.[9,10] The characterization of von Hippel-Lindau disease (vHL) as an autosomal-dominant condition predisposing carriers to the development of ccRCC, as well as hemangioblastomas, pheochromocytomas, and other vascular neoplasms, ultimately led to the discovery of repeated 3p deletions in ccRCC and eventually identification of the *VHL* gene through family-based linkage studies.[7,11,12] The gene has been mapped to 3p25,[13] contains three exons, and encodes a protein, pVHL, with 213 amino acid residues.[7,13,14] Inheritance of an inactivating germline mutation in *VHL* causes VHL disease, of which there are two major subtypes with higher and lower risk for pheochromocytoma.[15,16]

The *VHL* gene product, pVHL, has numerous functions. Its major function is as the substrate recognition module of an E3 ubiquitin ligase complex facilitating the oxygen-dependent ubiquitnation of the hypoxia-inducible factors (HIFs) has been well-characterized and implicated as its connection to the molecular pathophysiology of ccRCC.[17–21] HIFs are transcription factor heterodimers composed of an unstable α subunit and a stable β subunit, which regulate the expression of more than 1,000 target genes through binding to hypoxia response elements, which regulate genes such as the vascular endothelial growth factor (*VEGF*). In the presence of normal oxygen tension in the tissue microenvironment, pVHL targets the HIFα subunits, predominantly isoforms HIF1α and HIF2α, for destruction, recognizing the O_2-dependent post-translational hydroxylation of two proline residues. In the presence of low oxygen tension, pVHL does not recognize HIFα as a substrate for ubiquitnation and HIFα levels rise in the cell, resulting in the formation of the heterodimers, which promote the transcription of hypoxia response elements (Figure 1). HIFs target genes that are activated on engagement of a proximate hypoxia response element that may be located in the promoter, 5′ or 3′ untranslated regions, or even in intronic regions.

Bi-allelic *VHL* loss, either through mutation, hypermethylation, or chromosomal loss, is found in most

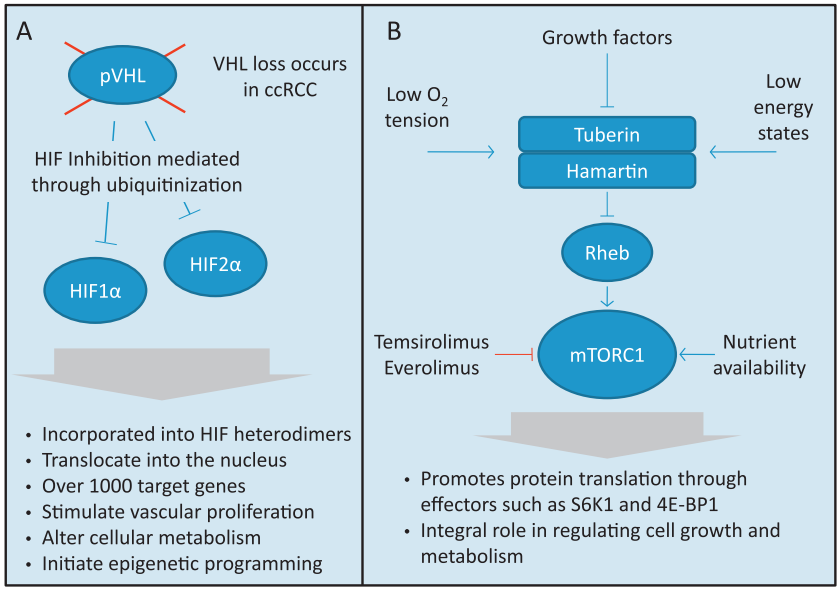

Figure 1. (A) The VHL-HIF axis. VHL loss occurs in the vast majority of ccRCCs. Without the inhibitory influence of pVHL, HIF1α and HIF2α levels rise. HIFα subunits are incorporated into heterodimeric transcription factors that lead to the transcription of more than 100 target genes. (B) The mTORC1 pathway. mTORC1 promotes protein translation involved in the regulation of cell growth and metabolism. Regulation of mTORC1 is tightly coordinated through the TSC complex (a heterodimer formed from tuberin and hamartin) and Rheb and is influenced by energy states and nutrient availability, the presence of growth factors, and oxygen tension.