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The Genetic Basis of Kidney Cancer: Implications for Management and Use of Targeted Therapeutic Approaches

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Each year there are over 270,000 cases and 115,000 deaths from kidney cancer worldwide. [1] Although localized kidney cancer is most often treated successfully with surgery, patients who present with advanced disease have a two year survival of less than 20%. Kidney cancer is not a single disease; rather, it is comprised of a number of diseases, each of which has a different genetic cause, a clinical course that can be predicted on the basis of genotype, a different histology, and a unique response to therapy. Fifteen genes, including *VHL*, *MET*, *FLCN*, *fumarate hydratase (FH)*, *succinate dehydrogenase (SDH)*, *TSC1*, *TSC2*, *PTEN*, *TFE3*, *TFEB*, and *MITF* have been found to cause or to be associated with the development of either sporadic or inherited forms of kidney cancer. [2;3]

In the last five years, there has been considerable progress in the development of therapeutic approaches that target the VHL pathway in clear cell kidney cancer. Seven novel agents, sunitinib, sorafenib, bevacizumab, temsirolimus, everolimus, pazaponib, and, just recently, axitinib have been approved in the U.S. for the treatment of patients with advanced kidney cancer. However, while these exciting targeted therapeutic agents have benefited many patients, there are currently few documented complete responses to therapy with the use of any of these agents, and most patients eventually develop progressive disease. Understanding the genetic basis of cancer of the kidney has been the critical foundation that has led to improved methods for molecular diagnosis and to the development of targeted approaches to therapy for various kidney cancers.

In the early 1990's the gene for the hereditary form of clear cell kidney cancer associated with von Hippel-Lindau (VHL) was identified.[4] Significant insight about growth rates as well as metastasis rates of *VHL* gene mutation-associated clear cell kidney cancer has been gained from the longitudinal studies of patients with VHL-associated kidney cancer. In careful follow-up of hundreds of patients with VHL-associated clear cell kidney cancer managed over a 20-year period, no patient on active surveillance using highly sensitive imaging techniques developed metastases when kidney tumors were removed surgically before the largest tumor grew to a 3 cm diameter size. In VHL patients, these tumors had a known genetic mutation of the VHL gene. Clear cell kidney cancer makes up approximately

75% of the cases of sporadic, non-inherited kidney cancer. The *VHL* gene has been found to be mutated (or silenced by methylation) in 80-90% of tumors from patients with sporadic, non-inherited kidney cancers.[5] The genes that cause non-VHL mutated clear cell kidney cancer are not yet known. Recently, histone modifying genes, including *PBRM1*, were found to be mutated in a significant subset of clear cell kidney cancers.[6] Clear cell kidney cancers have also been found in patients with germline mutations of *TSC1/TSC2*, *FLCN*, and *fumarate hydratase*., but patients with these genotypes more commonly present with different histologic patterns, including papillary cancer.

In an article entitled “Clinical, Molecular, and Genetic Correlates of Lymphatic Spread in Clear Cell Renal Cell Carcinoma” (European Urology, In Press), Kroeger, et al. report analysis of immunohistochemical staining profiles on 196 randomly selected kidney cancers from 1989-2000 and cytogenetic characterization of 272 clear cell kidney cancers from 1989 to 2007 in order to characterize the determinants of lymphatic spread. Analysis of the immunohistochemical staining revealed a strong correlation between decreased CAIX (carbonic anhydrase IX) and CAXII in conjunction with increased VEGFA, VEGFR1, VEGFR2 and p36 and lymphatic metastasis. Karyotypic analysis revealed a strong association between loss of chromosome 3 and a decreased incidence of lymphatic metastases. *CAIX* is a carbonic anhydrase gene that has been shown to be up-regulated in *VHL*-deficient cells. The *VHL* gene is on the short arm of chromosome 3 and chromosome 3p loss is highly associated with *VHL* gene mutation in clear cell kidney cancer. The finding by Kroeger et al. of an inverse relationship between CAIX expression and chromosome 3 loss and an increase in lymphatic metastases is consistent with their findings and those of others that clear cell kidney cancers with *VHL* gene mutations confer a better prognosis than do clear cell kidney cancers which lack a *VHL* gene mutation (*VHL* wild-type).[7] Clear cell kidney cancer without a *VHL* gene mutation is simply a different disease than clear cell kidney cancer with *VHL* gene mutation. Those with *VHL* gene mutations have a predictable growth and metastasis rate, as indicated by the findings from the longitudinal studies in the *VHL* patients with clear cell kidney cancer. The clear cell tumors without *VHL* mutations, on the other hand, much more aggressive cancers.

Active Surveillance

The findings reported here have implications in a number of areas, including the merits of using active surveillance as a management approach. Active surveillance of small renal tumors becoming a more widespread approach. However, in a number of trials of active surveillance of small renal tumors, a small but real percentage of metastases (and deaths) have been reported. If a patient with a small renal tumor (< 3 cm) were managed with active surveillance and the tumor turned out to be, for example, type II papillary kidney cancer, the result could be disastrous. If a patient with a small renal tumor that was clear cell histologic type without *VHL* gene mutation, the progression/metastasis rate could be hard to predict, but results would likely be poor. In contrast, the progression/metastasis rates in patients managed with active surveillance in *VHL*-deficient clear cell carcinoma is very predictable; however, the results from Kroeger, et al. in this and previous studies show that the *VHL* +/- tumor have a greater propensity to metastasize and are associated with a poor survival rate. If the tumor had, for example, a mutation of the Krebs cycle enzymes *FH* or *SDH*, the

likelihood of early metastasis would be much greater than with a *VHL* $-/-$ tumor. Kroeger, et al. appropriately suggest that criteria other than size alone should be considered for identification of subjects that can benefit from active surveillance; the most certain prognosis can be derived from knowing the genotype.

Surgical Management of Renal Tumors

The finding that lymphatic metastases correlated with primary T stage, but not tumor size, is an important finding that has implications for not only the basic biology of the cancer, but also the surgical management of renal tumors. The surgical approach to the management of renal tumors should be significantly influenced by both the pathology as well as the genotype. For example, a small clear cell renal tumor with a *VHL*, *MET* or *FLCN* mutation can most often be safely managed by partial nephrectomy with a small margin of normal renal parenchyma. However, there have been numerous incidences of small tumors that were managed by minimally invasive partial nephrectomies, in which either the tumor histology was not clear cell or the tumor did not have a *VHL* mutation, and the patient developed locally advanced or advanced disease. For example, when a patient with a *FH* or *SDH* mutation, regardless of the histology, presents with a small renal tumor, wide surgical incision is recommended and an open surgical removal versus a minimally invasive approach should be considered.

Targeting the Metabolic Basis of Kidney Cancer

The finding that nodal metastases in this very large data set correlated clearly with T stage, sarcomatoid features, Furman grade and microvascular invasion (which has previously been shown by this group to correlate with survival, along with *VHL* mutation status and *CAIX* expression) indicates that clear cell kidney tumors with nodal metastases are very metabolically active. The lymphatics are a source of lipids and fatty acids [8] that are critical to the growth of highly metabolically active kidney cancer. We have recently shown that fumarate hydratase-deficient kidney cancer is characterized by aerobic glycolysis; thus, *FH*-deficient kidney preferentially utilizes glucose instead of oxidative phosphorylation for ATP generation. In this process, activation of AMPK, the central energy sensor of the cell, is suppressed and mTOR (pS6) and fatty acid synthesis are activated to provide for rapid anabolic growth of this cancer. [9] In a related study of the metabolic basis of this form of kidney cancer, Mullen, et al. described a dominant glutamine-dependent reductive pathway in which glutamine was redirected into lipid biosynthesis to support this rapidly growing cancer.[10] The ready availability of lipids and fatty acids in the adjacent draining lymphatics of the kidney could serve as a source for the high energy nutrients that provide for the needs of highly aggressive forms of kidney cancer, and this availability could explain the association of lymphatic spread and poor survival. Understanding the metabolic pathways of kidney cancer provides the foundation for the development of novel approaches to therapy, such as targeting glutamine transport and glucose metabolism, which will hopefully lead to the development of more effective forms of therapy for patients with this cancer.

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