Multifocal Renal Cancer: Genetic Basis and Its Medical Relevance

Commentary on Jones et al., p. 7226

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More than 36,000 new cases of kidney cancer, accounting for 3% of all adult malignancies, are projected to be diagnosed in the United States in 2005, the majority of which are RCC. Furthermore, over 12,000 deaths annually in the United States are attributed to RCC, and the overall incidence of RCC has increased over the last 20 years (1). Kidney cancer is classified into four main types according to clinical and histologic criteria. The most prevalent form, clear cell RCC, accounts for 75% of the cases, and papillary renal carcinoma (PRC) accounts for 15%, chromophobe for 5%, and oncocytoma for 5%. PRC is further classified into type 1 (5% of cases) and type 2 (10% of cases) based on additional clinical, histologic, and genetic criteria (2–4). Cytogenetic alterations, including the gain of two or more of chromosome 7, 12, 16, 17, or 20 and loss of the Y chromosome in men, further distinguish PRC from clear cell RCC (4). Alterations that are characteristic of clear cell RCC, such as loss of the short arm of chromosome 3, are not typically observed in PRC (2–5).

Multifocality (or multicentricity) of tumors in a single organ occurs in a significant number of RCC cases: small (including radiologically undetectable) tumors have been found in up to 25% of kidneys resected by radical nephrectomy (6). Concern over the malignant potential of these small lesions no doubt lent support to radical nephrectomy as the ultimate standard of care for RCC for many years. Nonetheless, progress on a variety of fronts has brought nephron-sparing surgical techniques into more widespread use and reignited concern over the risk of leaving behind small but potentially malignant lesions. In this issue of Clinical Cancer Research, Jones et al. (7) address the question of whether multifocal papillary renal tumors in the same kidney arise from a single precursor lesion or independently, with the overall goals of improving risk assessment for smaller tumors that might remain after nephron-sparing surgery and improving our understanding of the biology of renal cell carcinoma (RCC).

A cornerstone of the progress that has popularized nephron-sparing surgery is greater knowledge of the molecular biology of renal cancers facilitated largely by the study of hereditary renal cancer syndromes, including von Hippel-Lindau (VHL), hereditary PRC (HPRC), Birt-Hogg-Dubé, and hereditary leiomyomatosis and renal cell cancer (2, 3). Each of these syndromes carries a varying risk of renal cancer and most are associated with characteristic tumor histology (Fig. 1) and associated clinical abnormalities (8). Renal masses in hereditary renal cancer syndromes tend to be bilateral, multifocal, and recurrent. For these patients, clinical management is focused on the prevention of metastatic disease, preservation of renal function, and minimization of the number of operations patients must undergo (8, 9). Much has been learned from the long-term management of VHL patients, where the refinement and selective implementation of nephron-sparing surgical techniques and minimally invasive approaches, such as cryotherapy and radiofrequency ablation, have been shown to lower morbidity, the risk of metastasis, and the need for hemodialysis or renal transplant, each associated with significantly higher morbidity and mortality (8). Coupled with these surgical advances are vastly improved and increasingly available imaging methods. Small renal tumors are now being discovered in younger, asymptomatic individuals, resulting in further scrutiny of radical nephrectomy as a first-line therapy as well as concern over the malignant potential of small lesions left behind (6).

Whereas multifocality in hereditary renal cancers is linked to the underlying germ line genetic defect, less is known about the genetic basis of multifocal sporadic RCC. Prior studies of this subject addressed multifocality in clear cell RCC, the most prevalent renal cancer type. Again, general insights into molecular mechanisms of tumorigenesis gained from the study of VHL, where RCC is also of the clear cell type, aided the subject addressed multifocality of sporadic clear cell RCC represent critical steps forward, one reported by Miyake et al. (10) and the other by Junker et al. (11), and each pointed to the same conclusion: in the vast majority of cases, there was a common clonal origin for multifocal clear cell tumors. Early studies, including that of Miyake et al., revealed similar patterns of chromosomal alterations by cytogenetic analysis and comparative genomic hybridization. These findings, including the common loss of heterozygosity on chromosome 3p characteristic of VHL as well as sporadic solitary clear cell renal tumors, were suggestive of both malignant potential and, further, a common cellular origin. Junker et al., whose earlier studies also included karyotyping and comparative genomic hybridization, later solidified the conclusion of clonal origin at the molecular genetic level by microsatellite analysis (11).

Armed with this knowledge, Jones et al. framed the present study of the genetic relationship among multifocal papillary renal tumors (7). Additional guidance was again available from the study of hereditary renal cancers: different tumor histologies were indicative of different underlying genetic and molecular mechanisms of tumorigenesis; thus, the malignant potential and common origin of multifocal clear cell tumors could not be extended to papillary renal tumors a priori. HPRC, characterized by a predisposition to develop multiple macroscopic and microscopic bilateral papillary renal tumors (12), is the hereditary counterpart of the sporadic type 1 papillary cancer recognized earlier by
Kovacs et al. (4). Through linkage analysis of an extended set of HPRC families, Schmidt et al. (13) localized the HPRC gene to chromosome 7q31-34, identified missense mutations in the MET gene within this region that were homologous to those in other receptor tyrosine kinase proto-oncogenes mutated in human neoplasias, and proposed that gain-of-function mutations in MET promote tumorigenesis in HPRC type 1 (Fig. 2).

The MET gene encodes the hepatocyte growth factor/scatter factor (HGF/SF) receptor protein tyrosine kinase, c-Met (14). HGF/SF is a potent mitogen, motogen, and morphogen secreted by cells of mesenchymal origin. c-Met is typically expressed in epithelial cells, and paracrine HGF/SF signaling via c-Met is important for normal embryonic development as well as adult homeostasis (15, 16). Although the role of HGF/SF in adult renal physiology is not yet completely understood, the kidney is an important source of circulating HGF/SF, and a growing body of evidence suggests that it is an endogenous renoprotective factor with potent antifibrotic activity (16). Among the many genes up-regulated by the HGF/SF pathway is that of the receptor itself, creating the potential for c-Met overexpression in otherwise normal target cells through persistent ligand stimulation (17); c-Met overexpression is widely observed in cancers of epithelial origin (17, 18). Intriguingly, trisomy of chromosome 7, where both MET and HGF genes are located, occurs with high frequency in PRC as well as in HPRC type 1 (19). HGF/SF and c-Met have been implicated in a variety of human malignancies other than HPRC largely through overexpression as well as through somatic mutation in some cases (17, 18). Importantly, the c-Met pathway activates a program of cell dissociation and increased cell motility coupled with increased protease production that has been shown to promote cellular invasion through extracellular matrices, and that closely resembles tumor metastasis in vivo (17, 18). In addition, pathway activation in vascular cells stimulates tumor angiogenesis, facilitating tumor growth for cancers that are growth limited by hypoxia and promoting tumor metastasis (18). Hypoxia alone up-regulates c-Met expression and enhances HGF/SF signaling in cultured cells and mouse tumor models (20).

Jones et al. did loss of heterozygosity analysis on multiple papillary tumors obtained following radical nephrectomy in 21 patients using six microsatellite markers for putative tumor suppressor genes (7). An overwhelming majority (95%) of the cases showed allelic loss in one or more papillary lesions for at least one of the polymorphic markers analyzed, but concordant allelic loss between coexisting tumors occurred in only a few (5%) of the cases (7). Fluorescence in situ hybridization showed that the majority of tumors analyzed (12 of 13) had gains of chromosomes 7 and 17 (7), consistent with results reported previously for PRC and HPRC (19). These results indicate that, unlike clear cell RCC, multifocal sporadic papillary tumors probably arise independently (i.e., early intrarenal metastasis does not seem to be the basis for papillary RCC multifocality). The findings further reinforce the importance of distinguishing between RCC subtypes at the time of diagnosis. Computed tomography (CT) imaging studies of HPRC type 1 tumors generally show hypoenhancement following i.v. administration of a contrast agent, unlike clear cell RCC that are typically hypervascular and hyperenhancing in dynamic contrast CT (21). Serial imaging of RCC patients can provide reliable estimates of tumor growth rate as well as changes in multifocality (21).

What impact does this information have on risk assessment in leaving behind small multifocal tumors after partial nephrectomy? Some guidance in the management of metastatic risk for sporadic multifocal clear cell RCC can be gleaned from the clinical management of VHL RCC patients, where the high morbidity and mortality associated with renal replacement therapy prompted researchers to adopt the strategy of following patients closely with serial imaging until the largest tumor was ≥3 cm in diameter before intervention, regardless of the number or pattern of tumors (22). Outcomes of 108 patients with VHL and whose renal tumors were <3 cm at the time of presentation managed using this strategy were compared with those of a group of 73 patients with VHL and tumors larger than 3 cm at the time of diagnosis (22, 23). Median follow-up for both groups was ≥5 years. In the group of patients with tumors less than 3 cm at presentation, no

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**Fig. 1.** Kidney cancer is not a single disease; it is made up of several different types of cancer, with different histologic types and different clinical courses, and caused by alteration of a different gene. FH, fumarate hydratase; BHD, Birt-Hogg-Dubé.
patients developed either metastatic disease or end-stage renal disease. Thirty-four percent (37 of 108) of these patients were managed with observation alone, as they did not develop tumors larger than 3 cm during the study period. Metastatic renal cancer developed in 27% (20 of 73) of patients with renal tumors larger than 3 cm at the time of presentation. The authors concluded that the strategy of observing tumors until renal tumors larger than 3 cm at the time of presentation. The authors concluded that the strategy of observing tumors until they reached a 3-cm threshold provided good cancer control while preserving renal function, and the strategy has become more widely accepted (23). This strategy should not be extended a priori to solitary clear cell RCC or papillary RCC, but when nephron-sparing surgery is elected in the treatment of multifocal PRC, serial imaging at regular intervals should be used to assess subsequent changes in tumor growth rate and/or number. Although the independent origin of multifocal papillary tumors does not imply that these tumors are capable of spreading at a relatively early stage, polyomy of chromosomes 7 and 17 is suggestive of some commonality in the mechanism of tumorigenesis (with possible overexpression of MET) and thus some malignant potential, and warrants conservative judgment in weighing surgical options for patients with sporadic multifocal PRC.

In summary, clear cell and papillary RCC are histologically, genetically, and mechanistically distinct; thus, distinct strategies must be used in clinical management, including assessment of the risk of metastasis. The study of hereditary renal cancer syndromes has accelerated our understanding of the molecular basis of tumorigenesis for these diseases and, to some extent, their sporadic counterparts, although clearly further research is needed. The mechanistic basis of multifocal tumorigenesis in HPRC and sporadic PRC, including a better understanding of the role of HGF/SF signaling in this process and in adult homeostasis, will aid in the refinement of clinical management strategies as well as in the development of efficacious molecularly targeted therapies. At the same time, ancillary biological studies rooted in this knowledge should help identify surrogate markers predictive of disease stabilization, progression, and metastasis.

References
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