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Impact of Genetics on the Diagnosis and Treatment of Renal Cancer

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Abstract

Kidney cancer is a heterogeneous disease comprised of a number of histologic subtypes, each associated with unique genetic mutations, clinical features, and sensitivity to treatment. By examining families affected with the hereditary kidney cancer syndromes von Hippel-Lindau, hereditary papillary renal cell carcinoma, hereditary leiomyomatosis and renal cell carcinoma, and Birt-Hogg-Dube', researchers have been able to identify the genes responsible for these syndromes. This work has revealed that kidney cancer is fundamentally a metabolic disorder, and as such, novel targeted therapies specific to their molecular biology have been developed and employed in both the hereditary and sporadic forms of renal cell carcinoma.

Keywords

Kidney cancer; Genetics; VHL; HPRC; HLRCC; BHD; Clear cell; Papillary; Chromophobe

Introduction

Renal cell carcinoma (RCC) is among the most common adult malignancies in the United States (ranking seventh in men and eighth in women) with approximately 58,240 new cases and 13,040 deaths expected in 2010 (1). The incidence of kidney cancer is rising, at least in part due to increased use of cross-sectional imaging, such as CT scans and MRIs (2). Despite increased detection and subsequent treatment, the mortality rate associated with this disease has not declined (3). When discussing the incidence and mortality associated with RCC, one must be mindful that it is not a homogenous entity. A number of malignant histologic subtypes, such as clear cell, papillary, and chromophobe are recognized by the Heidelberg classification system (4). (Figure 1) Each RCC subtype is associated with unique genetic mutations, clinical characteristics, and sensitivity to treatment (5, 6). (Table 1)

The systemic management of advanced and metastatic RCC has been drastically altered over the past five years with the approval of a number of targeted therapies, supplanting cytokine-based therapies as the treatment of choice for the majority of patients with clear cell RCC (7, 8). The optimal treatment for patients with non-clear histologies, however, remains undefined. Studying the genes underlying the various forms of RCC has shown that kidney cancer is a group of fundamentally metabolic disorders and revealed opportunities for enhanced diagnosis and novel targeted therapies.

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However, with the use of genetic testing for cancer susceptibility comes great responsibility to ensure that patients and research subjects are properly consented about the testing process and its myriad implications. The American Society of Clinical Oncology (ASCO) issued its initial recommendations about inherited cancer risk in 1996 with additional updates in 2003 and 2010 (9). ASCO advocates extensive pre- and post-test counseling that examines the implications of both a positive and negative result; discusses the potential impact on children and family members; reviews confidentiality and non-discrimination protections; provides options for prevention, surveillance, or treatment; and outlines concrete plans for post-test follow-up. A certified genetic counselor is an invaluable addition to any multidisciplinary team that is using genetic testing or investigating cancer syndromes such as those involved with hereditary kidney cancer.

Clear Cell Renal Cell Carcinoma

Clear cell RCC is the most common histologic subtype of RCC and accounts for approximately 75% of kidney cancer diagnoses (10). It also serves to illustrate the impact genetics has had on the diagnosis and treatment of renal cancer. Clear cell RCC is seen in von Hippel-Lindau (VHL) disease, which is an autosomal dominant hereditary cancer syndrome affecting approximately 1 in 36,000 live births (5, 11, 12). The disease manifests itself through kidney tumors, adrenal pheochromocytomas, retinal angiomas, central nervous system hemangioblastomas, pancreatic cysts and neuroendocrine tumors, endolymphatic sac tumors, and epididymal and broad ligament cystadenomas. In terms of renal involvement, VHL patients may develop up to 600 tumors and 1,100 cysts per kidney, making metastatic RCC the most common cause of mortality in this patient population (11, 12).

By performing genetic linkage analyses in patients afflicted with hereditary and sporadic kidney cancer, mutations in the *VHL* gene, which is located on the short arm of chromosome three and serves as a tumor suppressor, were identified (5, 13). With improved detection methods, germline mutations in the *VHL* gene are identifiable in nearly 100% of VHL families (14). Somatic *VHL* mutations are also identified in a high percentage of sporadic clear cell RCC tumors but are not seen in patients with non-clear histologies such as papillary, chromophobe, or collecting duct tumors (15). In patients with germline *VHL* mutations, the type and location of the mutation directly impacts the patient's phenotype; for instance, a higher incidence of RCC is seen in patients with partial vs. complete germline mutations (16–18).

The *VHL* gene encodes the VHL protein, which forms a complex with elongin B, elongin C, and Cul2 and targets the hypoxia-inducible factors, HIF1 α and HIF2 α , for ubiquitin-mediated degradation (19–21). The transcription factors HIF1 α and HIF2 α regulate a number of other genes involved in tumorigenesis, such as vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), epidermal growth factor receptor (EGFR), and glucose transporter (GLUT-1). (Figure 2) Under normoxic conditions, the VHL complex targets HIF for ubiquitin-mediated degradation, but under hypoxic conditions, the complex does not degrade HIF, allowing it to accumulate and drive the transcription of the downstream HIF-dependent genes. Likewise, in the case of clear cell RCC, a *VHL* gene mutation affecting the alpha domain, which binds elongin C/B and cul2, or in the beta domain, which targets HIF for degradation, results in an over accumulation of HIF and an increase in the downstream genes *VEGF*, *PDGF*, *EGFR*, and *GLUT-1* (22–27). Targeting these *VHL* transcription products have allowed novel agents such as sunitinib, sorafenib, bevacizumab, axitinib, temsorolimus and everolimus to be introduced against a disease that is notoriously resistant to cytotoxic chemotherapy and radiotherapy (8, 28, 29).

While these agents mark a major advance in the treatment of clear cell RCC, nearly every trial in which they were tested excluded the other histologic subtypes of RCC, providing clinicians and their patients little guidance when selecting a systemic treatment for non-clear cell RCC (30). The same methodology of studying the genetic and molecular characteristics of hereditary and sporadic non-clear cell RCC tumors has identified promising new pathways that are amenable to targeted therapy.

Papillary Renal Cell Carcinoma

Papillary RCC is the second most common histologic subtype of kidney cancer, accounting for approximately 10–15% of cases (10). It can be further separated histologically into papillary type 1 and 2 subtypes. Emerging data suggests that there may be significant differences in the genetics and molecular pathways underlying different types of papillary RCC as well as distinct survival outcomes associated with these entities (31). Researchers and clinicians must take these differences into account when they design targeted therapies and treatment protocols for patients with papillary RCC, such as ensuring adequate central pathology review as a study inclusion criterion.

Hereditary Papillary Renal Cell Carcinoma (HPRC) is a hereditary cancer syndrome in which affected individuals are at risk for the development of bilateral, multifocal, type 1 papillary renal carcinoma (32). HPRC is characterized by germline mutation of the proto-oncogene, *MET* (33, 34). Somatic mutations of *MET* have been found in a subset of tumors from patients with sporadic type 1 papillary kidney cancer (35). (Figure 3) These mutations result in ligand-independent activation of intracytoplasmic tyrosine kinase domains which constitutively activate the hepatocyte growth factor (HGF)/*MET* pathway (35–37). Families with hereditary papillary renal cancer (HPRC) harbor germline mutations in *MET*, usually accompanied by the nonrandom duplication of chromosome 7 bearing the mutated *MET* allele. The mutated *MET* is then passed to offspring in an autosomal dominant fashion with variable penetrance (38, 39).

Papillary type 2 tumors are now recognized as a distinct entity and occur both sporadically and in patients who have the familial syndrome of hereditary leiomyomatosis and renal cell carcinoma (HLRCC) (40). The genetic alteration associated with HLRCC has been localized to chromosome 1 and the gene identified as fumarate hydratase (*FH*). *FH* functions as a tumor suppressor, with both copies inactivated in tumors (41). The mutation is transmitted in an autosomal dominant pattern with high penetrance, placing patients with HLRCC at risk for developing papillary type 2 RCC, which is an especially virulent form of kidney cancer and prone to early metastasis (42, 43).

FH is a tricarboxylic acid (TCA or Krebs) cycle enzyme that plays a crucial role in aerobic cellular metabolism. The consequence of *FH* inactivation is the generation of a pseudo-hypoxic state, characterized by the upregulation of HIF, similar to that seen in the VHL pathway, although through a different mechanism. Inactivation of *FH* and the resultant accumulation of its substrate, fumarate, leads to competitive inhibition of HIF prolyl hydroxylase (HPH), which is a critical enzymatic regulator of intracellular HIF levels (44). (Figure 4) Inactivation of HPH interferes with hydroxylation of HIF at key proline residues and its subsequent recognition by the VHL complex, thus preventing VHL-dependent proteosomal degradation of HIFs. The resulting accumulation of HIF leads to transcriptional overexpression of proangiogenic factors such as VEGF as well as other genes such as transforming growth factor- α (TGF- α), PDGF and GLUT-1. This is an example of VHL-independent HIF accumulation in fumarate hydratase-deficient kidney cancer, resulting in increased amounts of growth factors (44). There is currently no well described sporadic counterpart to HLRCC-associated kidney cancer and no conclusive evidence that somatic

FH mutations play a significant role in sporadic kidney cancer tumorigenesis. However, the role of mutations in *FH* and other Krebs cycle enzymes, such as succinate dehydrogenase (SDH) in the genesis of sporadic papillary RCC, are under evaluation (45).

The definitive first-line treatment for advanced or metastatic papillary RCC has yet to be identified, but several agents are being investigated actively. Foretinib (also known as GSK1363089 or XL880) is an oral receptor tyrosine kinase inhibitor that targets c-MET and VEGFR2 and is being studied in a phase II multicenter trial (46).

Erlotinib is an oral EGFR tyrosine kinase inhibitor. A multicenter phase II trial of this agent in patients with locally advanced and metastatic papillary RCC reported an overall RECIST response rate of 11% (5/45 patients) with an additional 24 patients (53%) experiencing stable disease (47). Although this was a single-arm, uncontrolled study, the overall survival reported was higher than has been reported for patients with metastatic papillary RCC (48, 49). Addition of mTOR inhibitors or VEGF pathway antagonists may potentiate the single agent activity of erlotinib. A phase II trial of erlotinib in combination with bevacizumab, a monoclonal antibody against VEGF, is currently underway at the NCI and is one of the trials designed to evaluate this strategy (50).

Chromophobe Renal Cell Carcinoma

Chromophobe RCC accounts for approximately 4% of all RCC and is often detected while still confined to the kidney, as fewer than 5% of cases are metastatic at the time of diagnosis (10, 51, 52). The mechanisms underlying the genesis of this subtype of RCC are not well understood. However, studies focusing on Birt-Hogg-Dube' (BHD), a familial form of chromophobe kidney cancer, are beginning to provide insights that may help elucidate the molecular pathways driving this malignancy. BHD is an autosomal dominant hereditary cancer syndrome associated with bilateral, multifocal chromophobe RCC; approximately one-third of patients with BHD have this renal manifestation, with 5% demonstrating oncocytomas, and an additional 50% demonstrating hybrid chromophobe/oncocytic tumors (53, 54). The BHD gene, *FLCN*, is located on the short arm of chromosome 17 and was identified by genetic linkage analysis (55, 56). It is altered via insertion, deletion or nonsense mutations in the germline of >90% of affected individuals and has the characteristics of a loss-of-function tumor suppressor (57, 58). The function of *FLCN* and the consequences of its loss in chromophobe RCC are currently under study. The *FLCN* gene product complexes with folliculin-interacting proteins (FNIP1 and 2) and then binds AMPK, which is a component of the cellular energy sensing system and helps regulate mTOR activity (59, 60). (Figure 5)

Investigators have demonstrated mTOR activation in *FLCN*^{-/-} tumors, with activation of both mTORC1 and mTORC2 pathways (61). Additionally, the mTOR inhibitor, rapamycin, appears to lessen the renal manifestations of BHD and prolong survival in kidney-specific *FLCN*^{-/-} knockout mice.(62) These data suggest a role for mTOR inhibitors in the management of BHD associated tumors. The relevance of the BHD and mTOR pathways in sporadic chromophobe RCC are areas of active investigation; it is hoped that these studies will help identify rational targets and help determine the utility of mTOR inhibitors in this patient population (45).

Surgical Management

The tendency for patients with hereditary kidney cancer syndromes to develop bilateral, multifocal, recurrent disease has required the adoption of an aggressive approach to nephron-sparing surgery (NSS) in order to maximally preserve renal function. At the NCI, patients with VHL, HPRC, and BHD are observed with serial imaging (CT scan or MRI)

until their largest renal lesion becomes 3cm in size, which then triggers surgical intervention with NSS (63). Using this schema, no patient whose tumor was ≤ 3 cm at the time of surgery developed metastatic disease after more than 10 years of follow-up (64). Initial, repeat, and salvage NSS is performed using open, laparoscopic, and robotic approaches (65–67). While greater surgical morbidity is seen with serial interventions on the same renal unit, the increased overall mortality and cardiovascular morbidity associated with decreased renal function warrants the pursuit of partial nephrectomy over total nephrectomy whenever possible (68). In contrast to VHL, HPRC, and BHD, patients with HLRCC and renal lesions with any solid component are *not* observed. The aggressive nature of papillary type 2 RCC requires prompt surgical intervention (45).

Conclusion

Studying the gene pathways underlying VHL, HPRC, HLRCC and BHD have shown that kidney cancer is fundamentally a metabolic disorder. The kidney cancer genes elucidated thus far represent disorders of energy, nutrient, iron, and oxygen sensing (45). Novel targeted therapies specific to the molecular biology of each histologic subtype are under investigation and have potential to alter the course of advanced and metastatic RCC. Continued studies will be required to further advance the role of genetics in the management and treatment of renal cancer.

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Figure 1.
Histopathologically Distinct Malignant Renal Epithelial Neoplasms and their Incidence.
From Linehan, et al. with permission (5).

Figure 2.

The *VHL* gene complex targets hypoxia-inducible factors (HIF) for ubiquitin-mediated degradation. When there is a mutation in the *VHL* gene in clear cell kidney cancer, in either the elongin binding or HIF binding domain (A), HIF is not degraded and over-accumulates. Increased HIF levels lead to increased transcription of a number of downstream pathway genes that are thought to be important in kidney cancer, such as vascular endothelial growth factor (VEGF), glucose transport (GLUT-1), and transforming growth factor alpha (TGF- α) (B). Targeted approaches to therapy include tyrosine kinase inhibitors that target the downstream gene receptors (C). From Linehan et al. with permission (69).

Figure 3. Germline mutations in the tyrosine kinase domain of the proto-oncogene *MET* are found in Hereditary Papillary Renal Cancer patients, resulting in constitutive activation of the HGF/MET pathway. From Linehan, et al. with permission (5).

Figure 4.

HIF upregulation in fumarate hydratase (*FH*)^{-/-} cells: Under normoxic conditions, HIF is hydroxylated by HIF prolyl hydroxylase (HPH), which allows the VHL complex to recognize and target it for ubiquitin-mediated degradation in the proteasome. In HLRCC, the loss of *FH* shunts the TCA cycle to produce excess fumarate. Fumarate stabilizes HIF through competitive inhibition of HPH, preventing HIF hydroxylation and degradation. Elevated HIF drives transcription products involved with angiogenesis (VEGF), glucose transport (GLUT-1), and growth stimulation (TGF- α , PDGF). From Pfaffenroth et al. with permission (70).

Figure 5. The FLCN pathway. A) *FLCN* is the gene for the Birt-Hogg-Dubé (BHD) syndrome. Patients affected with BHD are characterized by germline mutation of the *FLCN* gene. The FLCN/FNIP1/FNIP2 complex binds AMPK and FLCN is phosphorylated by a rapamycin-sensitive kinase (i.e., mTORC1). B) When FLCN is deficient, AKT, mTORC1 and mTORC2 are activated. From Hasumi, et al. with permission (61).

Table 1

Hereditary Renal Cancer Syndromes

Syndrome	Chromosome	Gene	Renal Cancer Manifestation
Von Hippel-Lindau (VHL)	3p25	<i>VHL</i>	Clear cell renal cell carcinoma
Hereditary papillary renal carcinoma (HPRC)	7q31	<i>MET</i>	Papillary renal cell carcinoma type 1
Hereditary leiomyomatosis and renal cell carcinoma (HLRCC)	1q42–43	<i>FH</i>	Papillary renal cell carcinoma type 2
Birt-Hogg-Dube' (BHD)	17p11	<i>FLCN</i>	Hybrid oncocytic, chromophobe, and clear cell renal cell carcinoma; oncocytoma