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The Clinical Implications of the Genetics of Renal Cell Carcinoma

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Abstract

Over the last several decades, the advances in molecular genetics have elucidated kidney cancer gene pathways. Kidney cancer is a heterogeneous disorder. Each specific type of kidney cancer has its own histologic features, gene, and clinical course. Insight into the genetic basis of kidney cancer has been learned largely from the study of the familial or hereditary forms of kidney cancer. Extirpative surgery is currently the treatment of choice for kidney cancer that is confined to the kidney. Treatment for advanced or metastatic kidney cancer is a formidable challenge with the traditional therapies currently available. However, investigation of the mendelian single-gene syndromes, like von Hippel Lindau (VHL: *VHL* gene), hereditary papillary renal carcinoma (HPRC: *c-Met* gene), Birt-Hogg-Dubé (BHD: *BHD* gene), and hereditary leiomyomatosis renal cell cancer (HLRCC: fumarate hydratase gene) provides an opportunity to develop pathway specific therapies. Advances in molecular therapeutics offer novel treatment options for patients with advanced disease.

Keywords

Renal cell carcinoma; gene; VHL; BHD; HPRC; HLRCC

Introduction

It is estimated that 54,390 men and women in the United States will be diagnosed with kidney cancer, while 13,010 will die of their disease in 2008. This number can also be expressed as 1 in 72 men and women will be diagnosed with cancer of the kidney during their lifetime and this incidence continues to rise. (1) With the increased use of computed tomography and other imaging modalities, kidney tumors are being diagnosed at earlier stages, often as incidental lesions. The increased incidence cannot be explained entirely by the wider use of imaging. (2) Although extirpative surgery is often curative, 30% of patients will present with metastases at the time of initial diagnosis. In addition, 30% of initially organ-confined disease will develop metastases during follow-up at variable intervals. (3) Treatment of metastatic disease remains a formidable challenge in this day and age. Elucidation of the genetics basis of kidney cancer has given way to exciting new advances in molecular therapeutics for the treatment of metastatic kidney cancer.

Renal cell carcinomas are adenocarcinomas derived from renal tubular epithelium. Histologically, there are 5 subtypes: conventional (clear cell) (70–80%), chromophile (papillary) (10–15%), chromophobe (3–5%), collecting duct (1%), and unclassified (1%). Papillary is further classified into type 1 (5%) and type 2 (10% of cases) based upon further

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genetic alterations, histologic, and genetic criteria. (4;5) (4) (6) Renal cell carcinoma can be hereditary as well as sporadic or non-hereditary. While sporadic RCC is often a solitary lesion and most commonly present in individuals in their 60's, inherited forms tend to be multifocal, bilateral and have an early onset. Each subset has marked different clinical courses, is caused by different genes, and may have different responses to new therapeutics modalities.

In the early 1980s, the search to identify a loss of heterozygosity in one of the alleles of a cancer gene was initiated, with the hope that loss of heterozygosity would indicate the presence of a cancer gene at that location. A tumor suppressor gene requires loss of function or inactivation of one or both of the genes, often by mutation of one allele combined with deletion, or loss, of the second allele; whereas, an oncogene is activated by one change in the gene. In the initial studies, loss of segments at chromosome 3 in tumor tissue, suggested that a cancer gene for kidney cancer was present at this location. (7) Dr Knudson's "two hit" theory postulates that most tumor suppressor genes encode proteins responsible for the negative regulation of cellular growth. (8) A mutation that causes a loss of the function in one these proteins will lead to tumorigenesis or uninhibited cell growth. As the gene of interest for clear cell kidney cancer was too large to localize with the technology that was available at the time, an approach focusing on a hereditary form of kidney cancer, von Hippel Lindau, was used as the model of investigation. The hope was that the gene involved in hereditary kidney cancer may involve the same gene as in the sporadic form of kidney cancer.

von Hippel Lindau (VHL)

Von Hippel Lindau is a hereditary form of kidney cancer that is inherited in an autosomal dominant pattern with an incidence of 1 in 36,000 live births.(4) Clinical manifestations include the risk for development of renal cell carcinoma, pheochromocytoma, pancreatic cysts, endolymphatic sac tumors, papillary cystadenomas of the epididymis, retinal angiomas, and hemangioblastomas of the brain stem, cerebellum, or spinal cord. The tumors are highly vascular. With the recent improvement in the treatment of the central system manifestation, metastatic renal cell carcinoma has become the most common cause of mortality in these patients. The renal cell carcinoma is of the conventional clear cell type and may be solid or cystic. Patients are at risk to develop up to 600 microscopic tumors and over 1000 cysts per kidney.(9)

Consistent loss of the short arm of chromosome 3 in VHL associated kidney tumors was identified (10). Genetic linkage analysis was utilized to help identify the VHL gene which was identified on the short arm of chromosome 3p. (11) The loss of the single normal allele of the VHL gene in the kidney cancer cell samples was critical and suggested that there was an inherited gene at this location which was associated with the development of VHL-associated clear cell kidney cancer. Germline mutations on the VHL gene are identified in nearly 100% of VHL families. (12)

The different clinical manifestations of VHL can be associated with the location and type of the VHL gene mutation (13;14). Penetrance of the traits is far from complete, and for some, such as pheochromocytomas, they tend to be clustered in certain families but do not occur in others. (15) Maranchie, et. al., identified a significantly higher incidence of renal cell carcinoma in patients with partial germline VHL mutations versus those with complete VHL gene mutations. (16) It is now known that with mutation analysis (e.g. insertion, deletion, missense or nonsense) and the location (e.g. codon position) of the mutation, correlations can be made to the phenotype, i.e., the extent of involvement of the various organ systems affected by VHL. The VHL gene mutation has also been found in sporadic clear cell renal cell carcinoma using polymerase chain reaction (PCR) amplification. (17;18)

The function of the VHL gene has been evaluated extensively. It is a small gene that encodes 854 nucleotides on three exons and is responsible for encoding the VHL protein. (11) The VHL protein forms a complex with proteins including elongin C, elongin B and Cul-2 (19) (20), (21) and targets the alpha subunits of the hypoxia inducible factors, such as HIF- α and HIF-2 α , which are instrumental to ubiquitin-mediated degradation (22) (23). There are multiple downstream genes, such as Glut 1 (glucose transport), vascular endothelial growth factor (VEGF, blood vessel growth), epidermal growth factor (EGF), transforming growth factor (TGF- α), for which HIF regulates. The expression of these genes increased in clear cell carcinoma when the VHL gene is inactivated (Fig. 1). Many of the receptors for HIF-regulated genes are the targets for the new targeted therapeutic approaches for clear cell carcinoma. (24)

Hereditary Papillary Renal Carcinoma (HPRC)

Hereditary papillary renal carcinoma is an autosomal dominant hereditary cancer syndrome in which affected individuals are at risk of developing bilateral, multifocal type 1 papillary renal carcinoma, often at a late age of onset (50 to 70 years). (25) To date the kidney is the only organ to be affected in HPRC patients. The tumors are most often well differentiated; however, they are malignant and can metastasize. HPRC is a highly penetrant disease in which affected individuals are highly likely to develop bilateral, multifocal type 1 papillary kidney cancer. In the early reports this disease was described as having a late onset,(26;27); however, recently an early onset form of this disease has been described.(28) Radiographic interpretation of these lesions is difficult often due to their small size and poor enhancement on computed tomography which is attributed to their hypovascularity. Due to their hypovascularity, HPRC kidney tumors (and all type 1 papillary kidney tumors) may easily be misinterpreted as renal cysts. However, computed tomography is the imaging modality of choice as a screening tool due to its greater sensitivity in detecting these lesions. (29) Renal ultrasound may be very helpful in differentiating between a cyst and solid mass in a patient at risk for HPRC. Genetic evaluation of tumors in these families did not demonstrate abnormality on chromosome 3. Three years after describing the syndrome, researchers identified the gene responsible for HPRC on chromosome 7q31. (26;27) In this particular disease process activation of a proto-oncogene is the inciting event, not inactivation of a tumor suppressor gene, as is the case with VHL. Missense mutations in the tyrosine kinase domain of the *Met* proto-oncogene at 7q31 are responsible for constitutive activation of the MET protein in HPRC. The MET transmembrane protein is found at a receptor site for hepatocyte growth factor (also known as scatter factor). (30) Upon activation by hepatocyte growth factor, MET tyrosine phosphorylation induces the proliferation and differentiation of epithelial and endothelial cells, cell branching and invasion. (31) In sporadic papillary renal cell carcinoma, trisomy of chromosome 7, which contains HGF/SF and MET, occurs in 95% of patients. (32) In HPRC kidney tumors there is also trisomy of chromosome 7 and a non-random duplication of the chromosome bearing the mutated *Met* gene, implicating this event in tumorigenesis.(33) Molecular targeting approaches are being developed to inhibit the interaction of HGF and its receptor, and suppression of the downstream signaling cascade of activated c-MET. (5) These agents could then be used as a potential therapy for papillary renal cell carcinoma.

Birt Hogg Dube (BHD)

Birt-Hogg-Dubé is a hereditary cancer syndrome with an autosomal dominant inheritance pattern, in which affected persons are at risk to develop cutaneous fibrofolliculomas, pulmonary cysts, spontaneous pneumothoraces, and renal tumors. (34) The renal lesions are predominately derived from the distal nephron, and are bilateral and multifocal. The renal tumors are primarily chromophobe renal cell carcinomas (33%), hybrid tumors (50%) and oncocytomas (5%). Additionally, multifocal oncocystosis is evident in the surrounding normal

renal parenchyma in 50%. Other forms of renal cell carcinoma have been identified in this patient population, to include clear cell carcinoma. (35)

Genetic linkage analysis was performed and used to localize(36) and subsequently to identify the BHD gene to 17p11.2.(37) The gene product is folliculin, and is truncated as a result of insertions, deletions or nonsense mutations.(38) Further investigations have demonstrated the BHD gene has the characteristics of a tumor suppressor gene. (39) A high frequency of mutations in the wild type allele was found when DNA of 77 renal tumors from 12 patients with germline BHD mutations were analyzed, thus providing the second “inactivating hit”. Mutation analysis of the BHD gene in the germline of kindreds suspected of being affected with BHD provide an opportunity for accurate diagnosis of this disease.

Hereditary Leiomyomatosis Renal Cell Cancer (HLRCC)

A fourth inherited renal cell carcinoma syndrome, hereditary leiomyomatosis renal cell cancer (HLRCC) was described in 2001 by Launonen and colleagues. (40) Patients are at risk to develop cutaneous and uterine leiomyomas and an aggressive type of kidney cancer that is often confused with type 2 papillary or collecting duct RCC.(41) The renal tumors in this syndrome are often solitary and unilateral, and they are more likely to be aggressive and lethal if allowed to progress. Most patients will develop cutaneous leiomyomas, and in the case of women, most will have uterine fibroids at a young age, and may have had a hysterectomy prior to formal diagnosis of HLRCC. Penetrance for RCC is lower than for the cutaneous and uterine manifestations, with only a minority (20–35%) of patients developing RCC.

The HLRCC gene was mapped to a region on 1q42–44, and is the site of the fumarate hydratase gene. (42) Fumarate hydratase is an essential enzyme for the conversion of fumarate to malate in the Krebs cycle. The loss of FH function and impediment of the Krebs cycles impairs the Krebs cycle therefore giving way to glycolic metabolism and upregulation of HIF and HIF inducible transcripts (Fig. 2). (43) Subsequent germline mutations were found in 52/56 (93%) in HLRCC families. (44) Elevation of HIF and inactivation of fumarate hydratase are potential molecular therapeutic targets for treatment of this aggressive type of kidney cancer.

Treatment

Clinical management of patients with localized hereditary renal cancer has several goals: namely, preservation of renal function and prevention of metastatic disease. The tumors in these syndromes tend to be multifocal, bilateral and recurrent. Lessons learned from nephron-sparing surgery techniques applied to such patient with VHL can be translated into clinical management of sporadic multifocal renal cell carcinoma. Outcomes of 108 VHL patients whose renal lesions were less than 3cm were followed closely with serial imaging and were compared to 73 VHL patients with tumors larger than 3cm. Patients with lesions less than 3 cm did not develop metastatic disease. In contrast, 20 of the 73 (27%) of the patient with lesions larger than 3cm developed metastases. Median follow for both groups was greater than 5 years. (45) (46) Regardless, surgical extirpation remains the current standard for the treatment of localized renal cell carcinoma. The surgical options are many, and include, but are not limited to, open, laparoscopic, and robotic surgery, in addition to ablative techniques.

Due to the advances in the molecular and genetic biology of renal cell carcinoma, a paradigm shift has occurred in the treatment of patients with advanced renal cell carcinoma. While immunotherapeutic treatments such as interleukin-2 offer the only form of therapy which is associated with complete response, the majority of patients do not respond to this type therapy. (47) The identification of the VHL gene and its pathway has provided the foundation for targeted therapy for this disease.

Bevacizumab, a recombinant human monoclonal antibody to VEGF, has been shown to decrease angiogenesis in renal cell carcinoma by binding and neutralizing VEGF. (48) Other targeted agents, such as sunitinib, a small molecule tyrosine kinase inhibitor of VEGFR-2 and platelet derived growth factor (PDGFR-B), provide a rational approach in the treatment of clear cell kidney cancer. In a single arm, phase II trial of 106 cytokine refractory metastatic clear cell RCC patients, 34% of patients experienced a partial response with a median progression free survival of 8.3 months.(49) A phase III trial, conducted by Motzer, et. al., demonstrated in previously untreated metastatic RCC patients, progression free survival was 11 months versus 5 months in favor of Sunitinib over interferon alpha. (50)

Sorafenib is a Raf kinase inhibitor in addition to an inhibitor of VEGFR-2, VEGFR-3, and PDGFR-B. In a phase II, randomized discontinuation study, sorafenib was associated with a prolonged progression free survival, compared to placebo in patients with metastatic RCC. (51) A subsequent Phase III randomized trial demonstrated a significant prolongation of progression free survival versus placebo in patients with advanced clear cell renal cell carcinoma in whom had previously failed therapy. (52)

Conclusion

In summary, kidney cancer is a heterogeneous disease. As research continues and our understanding of the molecular genetics of renal cell carcinoma expands, improvement in the diagnosis, prevention and treatment of these malignancies is likely. Agents that target the VHL/HIF pathway in patients with advanced clear cell carcinoma have had encouraging results. Combination of therapies, i.e., use of agents that target multiple aspects of the pathway, are currently being studied.

Acknowledgments

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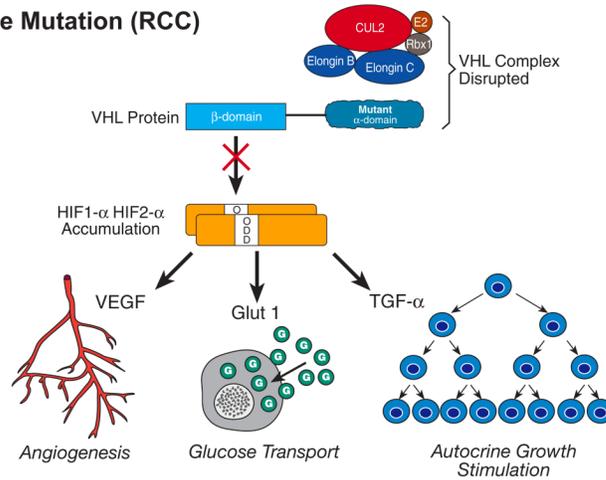
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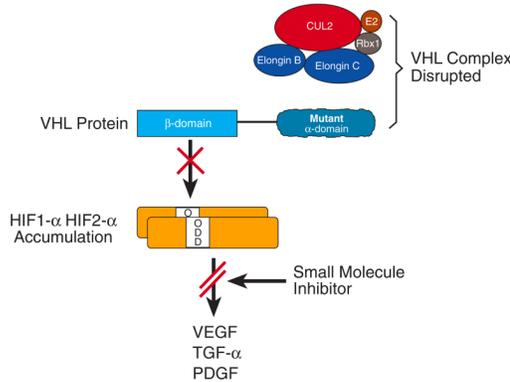
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A. VHL Gene Mutation (RCC)



B. VHL/HIF Pathway Molecular Targeting



C. VHL/HIF Downstream Pathway Molecular Targeting

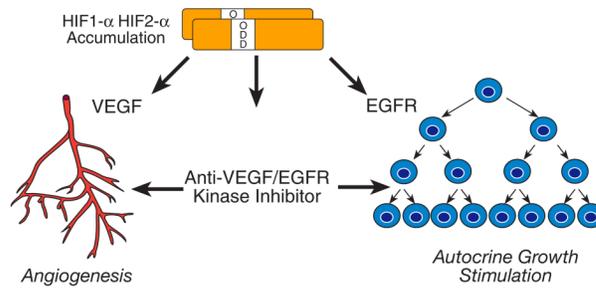


Fig. 1. The *VHL* gene complex targets hypoxia-inducible factors (HIF) for ubiquitin-mediated degradation. When there is a mutation in the *VHL* gene in clear cell kidney cancer, in either the elongin binding or the HIF binding domain (A), HIF is not degraded and this protein overaccumulates. Increased 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), the glucose transporter, GLUT1, and transforming growth factor α (TGF α) (B). Targeted approaches to therapy currently include tyrosine kinase inhibitors that target the downstream gene receptors (C). Other approaches being developed to target the

VHL-HIF pathway in clear cell kidney cancer include the development of small molecules or other agents which block HIF transcription. Reprinted from Linehan et al. [54].

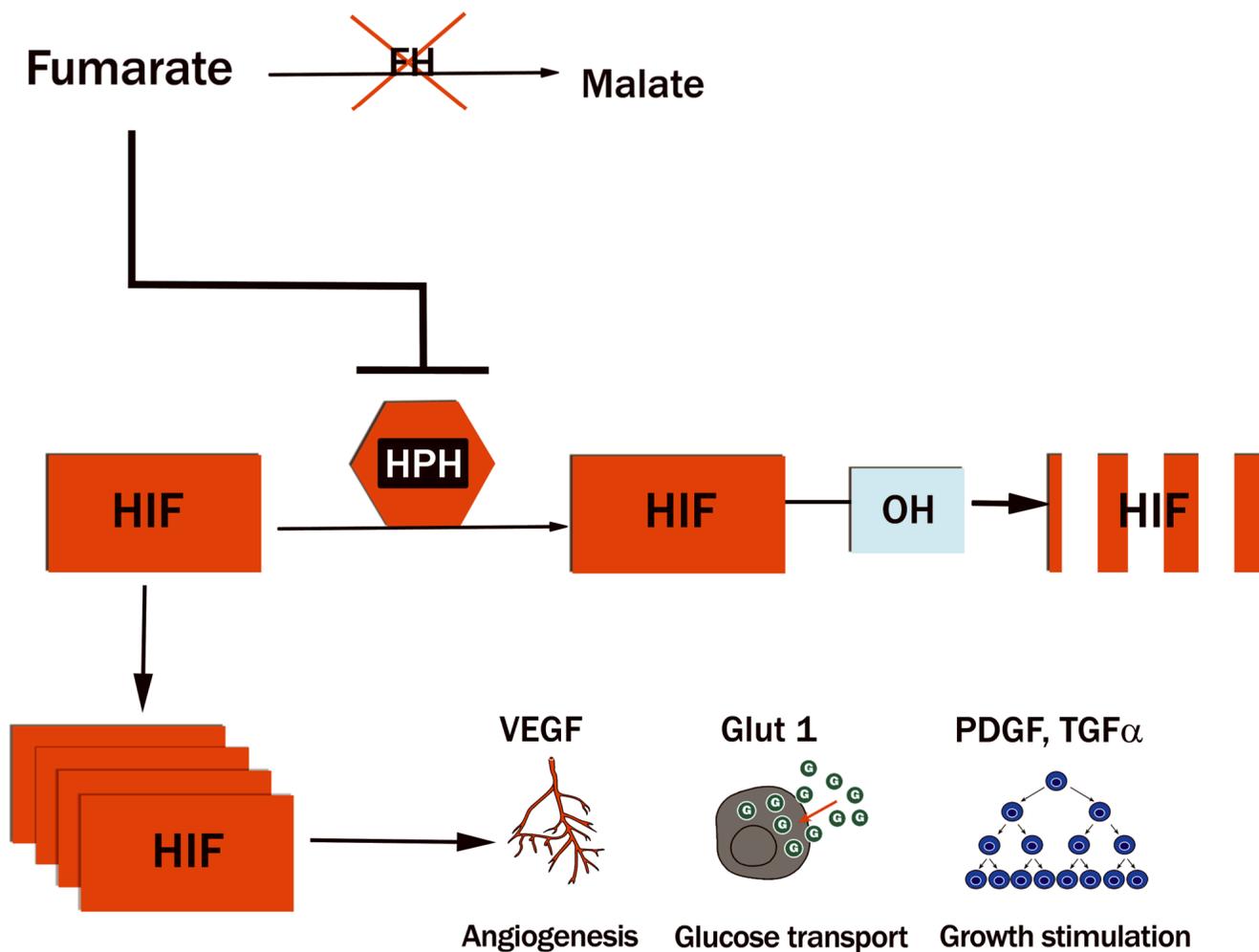


Fig. 2. Hereditary leiomyomatosis and renal cell cancer pseudohypoxia. Fumarate accumulates due to loss of FH activity. Rising fumarate levels inhibit HPH with concomitant upregulation of hypoxia response genes *VEGF* and *GLUT-1*. Reprinted from Sudarshan, et al.(53)