Genetic Basis of Cancer of the Kidney: Disease-Specific Approaches to Therapy

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ABSTRACT

Studies during the past two decades have shown that kidney cancer is not a single disease; it is made up of a number of different types of cancer that occur in this organ. Clear cell renal carcinoma is characterized by mutation of the *VHL* gene. The *VHL* gene product forms a heterotrimeric complex with elongin C, elongin B, and Cul-2 to target hypoxia-inducible factors 1 and 2α for ubiquitin-mediated degradation. *VHL*−/− clear cell renal carcinoma overexpresses epidermal growth factor receptor and transforming growth factor α. Both hypoxia-inducible factor 1α and the epidermal growth factor receptor are potential therapeutic targets in clear cell renal carcinoma. Studies of the hereditary form of renal cell carcinoma (RCC) associated with hereditary papillary renal carcinoma (HPRC) determined that the c-Met proto-oncogene on chromosome 7 is the gene for HPRC and for a number of sporadic papillary RCCs. The HPRC c-Met mutations are activating mutations in the tyrosine kinase domain of the gene. The gene for a new form of hereditary RCC (Birt Hogg Dubé syndrome) associated with cutaneous tumors, lung cysts, and colon polyps or cancer has recently been identified. Studies are currently under way to determine what type of gene *BHD* is and how damage to this gene leads to kidney cancer. Individuals affected with hereditary leiomyomatosis renal cell carcinoma are at risk for the development of cutaneous leiomyomas, uterine leiomyomas (fibroids), and type 2 papillary RCC. The *HLRC* gene has been found to be the Krebs cycle enzyme, fumarate hydratase. Studies are under way to understand the downstream pathway of this cancer gene.

INTRODUCTION

Kidney cancer affects 32,000 people each year and is responsible for nearly 12,000 deaths annually in the United States (1). Although there have been remarkable advances in the development of immunologic forms of therapy for this disease, currently there is still no effective form of therapy for most patients with advanced renal carcinoma. Those patients who present with advanced kidney cancer have a 2-year survival rate of <20% (1).

Genetic and clinical studies during the past two decades have shown that kidney cancer is not a single disease; it is made up of a number of different types of cancer that occur in this organ (2, 3). Each may have a distinct histologic type, have a different clinical course, respond differently to therapy, and be caused by alteration of a different gene (3). Kidney cancer occurs in an inherited form and a sporadic, noninherited form. To identify the genes that cause sporadic, noninherited cancer of the kidney, families with kidney cancer were studied to determine whether the genes that cause the inherited forms of renal cell carcinoma (RCC) might be involved in the development of the common forms of sporadic, non-inherited kidney cancer (Fig. 1).

VHL GENE: VON HIPPEL-LINDAU AND CLEAR CELL RENAL CARCINOMA

The most well-studied form of inherited clear cell renal carcinoma is that associated with von Hippel-Lindau (VHL) syndrome. Affected individuals in VHL kindreds are at risk for the development of tumors in the cerebellum, spine, retina, inner ear, pancreas, adrenal glands, and kidneys (4). The kidney cancer in VHL is uniformly clear cell renal carcinoma (5). Affected individuals are at risk for the development of up to 600 clear cell renal carcinomas per kidney (6).

Genetic linkage analysis performed in VHL kindreds (7) resulted in the identification of the *VHL* gene in 1993 (8). Subsequent studies revealed *VHL* gene mutation or methylation in a high percentage of tumors from patients with sporadic, noninherited clear cell renal carcinoma (9, 10). *VHL* gene mutation is not found in type 1 papillary renal carcinoma, type 2 papillary renal carcinoma, chromophobe renal carcinoma, collecting duct renal carcinoma, or oncocytoma (Fig. 2*A–D*).

The *VHL* gene has been found to have the characteristics of a tumor suppressor gene. In clear cell renal carcinoma in VHL patients and in a high percentage of tumors from patients with sporadic clear cell RCC, one inherited allele of the *VHL* gene is mutant, and the second allele is deleted (9, 11, 12). The product

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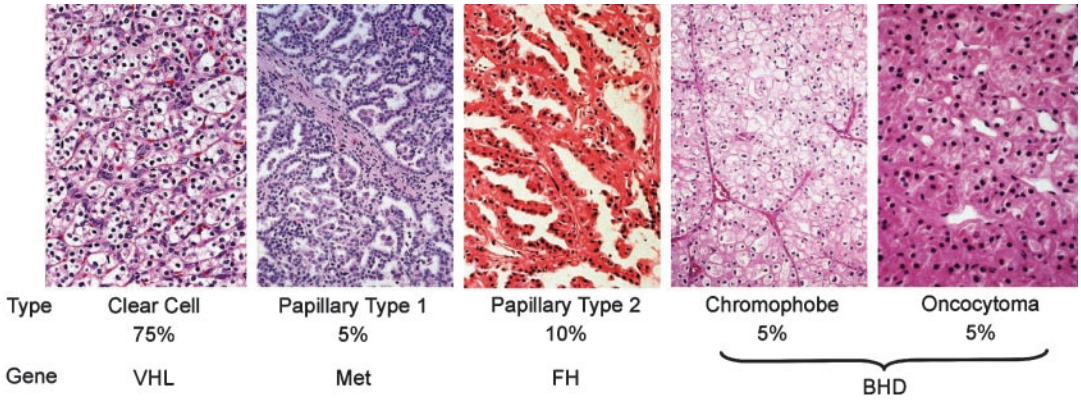

Fig. 1 Kidney cancer is not a single disease; it is made up of a number of different types of cancer, with different histologic types and different clinical courses and caused by alteration of a different gene. From Linehan *et al.* (3).

of this gene forms a complex with other proteins, including elongin C/B and Cul2 (13, 14), and targets the α-subunit of hypoxia-inducible factor (HIF)-1α and HIF-2α for ubiquitin-mediated degradation (15–20). Complex formation and degradation are normal processes that are hypoxia mediated. When the *VHL* gene is mutated, the complex cannot target and degrade HIF, which overaccumulates. The overaccumulation of HIF is associated with an increased transcription of such downstream targets as vascular endothelial growth factor (VEGF), GLUT1, platelet-derived growth factor, and transforming growth factor α. Understanding the VHL pathway and how damage to this gene leads to clear cell kidney cancer provide a unique opportunity for the development of disease-specific therapy for patients with advanced RCC.

THE *c-Met* GENE: TYPE 1 PAPILLARY RENAL CARCINOMA

In 1994, a previously undetected type of hereditary kidney cancer, hereditary papillary renal carcinoma (HPRC), was reported (21). Affected individuals in HPRC kindreds were found to be at risk for the development of bilateral, multifocal type 1 papillary renal carcinoma (22, 23). Genetic studies in HPRC kindreds led to the identification of the *c-Met* gene on chromosome 7 as the gene for HPRC (24). *c-Met* is an oncogene. Activating mutations in the tyrosine kinase domain of the c-Met were found (*a*) in the germ line of affected individuals in HPRC kindreds and (*b*) in a subset of tumors from patients with sporadic, type 1 papillary renal carcinoma (25). HPRC-associ-

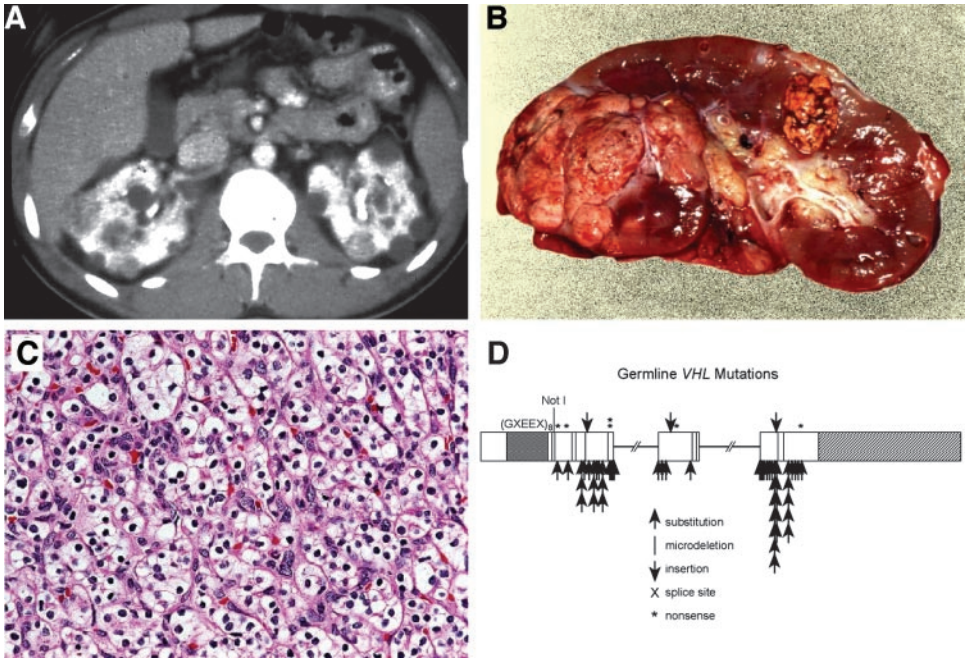

Fig. 2 The *VHL* gene is the gene for the inherited form of clear cell renal carcinoma associated with VHL and for common form of sporadic, noninherited clear cell renal carcinoma. Patients with VHL are at risk for bilateral, multifocal (*A* and *B*) RCC that is clear cell type (*C*). Reduced from ×40. VHL gene mutation is detected in germline of affected individuals in VHL kindreds (*D*). From Linehan *et al.* (3).

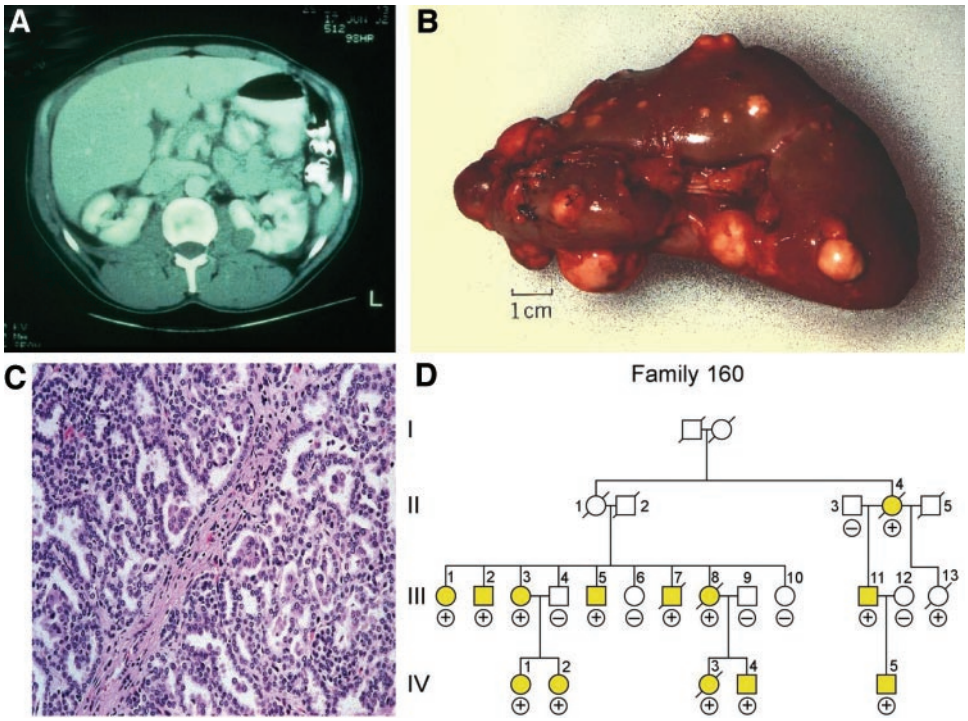

Fig. 3 HPRC is a hereditary cancer syndrome in which affected individuals are at risk for the development of bilateral, multifocal, type 1 papillary renal carcinoma (21). (*A*) CT of abdomen reveals multiple bilateral solid renal tumors. (*B*) Representative kidney demonstrates multiple, discrete tumor nodules of varying size. (*C*) Type 1 papillary histology characteristic of HPRC tumors (×200). (*D*) Pedigree of HPRC family 160 showing autosomal dominant pattern of inheritance. Closed symbols indicate affected individuals; open symbols indicate unaffected individuals. HPRC is caused by germ-line mutation of the *c-Met* gene (24). From Linehan *et al.* (3).

ated type 1 papillary renal carcinomas are characterized by trisomy 7 with a nonrandom duplication of the mutant *c-Met* allele (Fig. 3; ref. 26).

BHD GENE: CHROMOPHOBE RENAL CARCINOMA

Birt Hogg Dubé (BHD) is a hereditary cancer syndrome in which affected individuals are at risk for the development of cutaneous nodules (hair follicle fibrofolliculoma), pulmonary cysts, and bilateral, multifocal renal tumors (27–29). The tumors that occur in BHD patients may be chromophobe renal carcinoma (33%), chromophobe/oncocytic hybrid (50%), oncocytoma (7%), or clear cell renal carcinoma (5%). Genetic studies in BHD kindreds led to the localization and subsequent identification of the *BHD* gene (30). The *BHD* gene appears to have the characteristics of a loss of function tumor suppressor gene (31). Although studies are currently under way to determine how damage to this gene leads to chromophobe renal carcinoma, sporadic chromophobe renal carcinoma has been shown to overexpress c-Kit (32) Consequently, c-kit could provide a therapeutic target for this disease (Fig. 4).

FUMARATE HYDRATASE GENE: TYPE 2 PAPILLARY RENAL CARCINOMA

Hereditary leiomyomatosis RCC (HLRCC) is a hereditary cancer syndrome in which affected individuals are at risk for the development of cutaneous and uterine leiomyoma and an aggressive form of type 2 papillary renal carcinoma. The gene for HLRCC has been found to be the Krebs cycle enzyme fumarate hydratase (FH) (33). Mutations of *FH* are found in the germ line of affected individuals in HLRCC kindreds (34). *FH* appears to function as a tumor suppressor gene; loss of the second allele has been detected in kidney tumors from HLRCC patients. The type 2 papillary kidney cancer found in HLRCC patients is a particularly aggressive form of renal carcinoma, *i.e.*, it can metastasize early and is often fatal. Studies are under way to determine how damage to the Krebs cycle enzyme FH leads to the development of type 2 papillary renal carcinoma (Fig. 5).

TARGETING THE *VHL* PATHWAY: HYPOXIA-INDUCIBLE FACTOR TRANSCRIPTION

There are a number of potential approaches for targeting the VHL pathway in VHL−/− RCC. One potential approach is to block transcription of HIF. By use of a cell-based high-throughput screen for identification of small molecule inhibitors of the HIF-1 pathway, Rapisarda *et al.* (35, 36) have shown that the camptothecin analog topotecan inhibits HIF-1 transcriptional activity and HIF-1α accumulation in hypoxia-treated human glioma cells. Because *in vitro* and *in vivo* studies in human VHL−/− kidney cancer model systems suggest that HIF-2 is more critical to tumorigenesis than HIF-1 (19, 20, 37), intense efforts are under way to identify agents that affect the transcription of HIF-2 (as outlined in refs. 38–40).

TARGETS DOWNSTREAM OF HYPOXIA-INDUCIBLE FACTOR: VASCULAR ENDOTHELIAL GROWTH FACTOR, EPIDERMAL GROWTH FACTOR, AND PLATELET-DERIVED GROWTH FACTOR RECEPTORS

Another approach is to target pathways downstream of HIF, such as those triggered by receptors to VEGF, epidermal

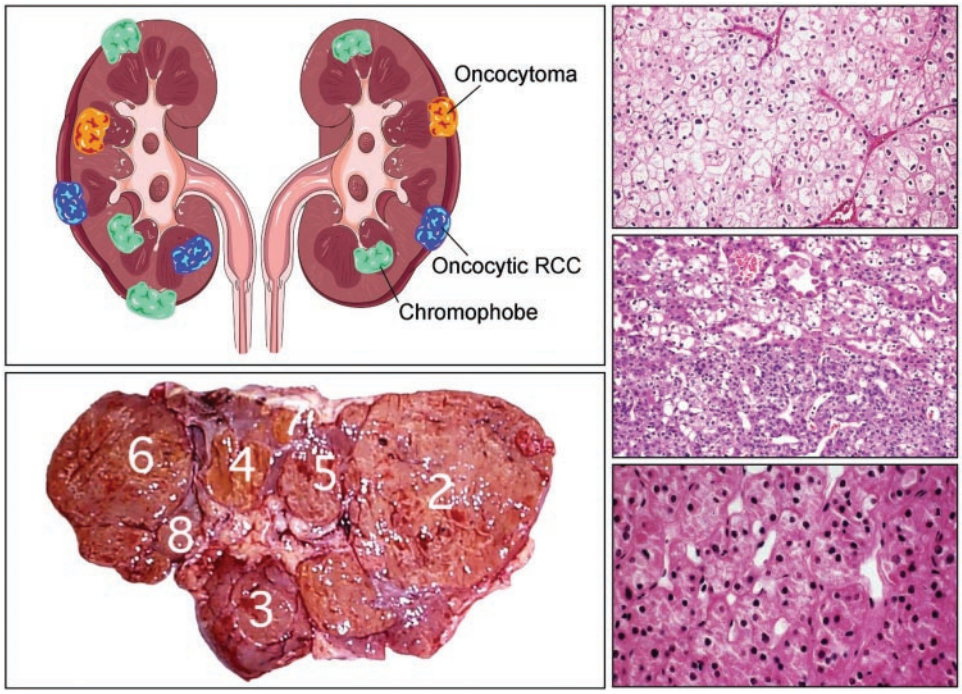

Fig. 4 Birt Hogg Dubé-associated kidney cancers. Birt Hogg Dubé is a hereditary cancer syndrome in which affected individuals are at risk for the development of chromophobe and oncocytic renal carcinoma and oncocytoma (28, 55). Individuals affected with BHD are at risk for bilateral, multifocal renal tumors (*left*). BHD associated renal tumors may be chromophobe renal carcinoma (*upper right*), hybrid-oncocytic neoplasms (*center right*) or oncocytoma (*lower right*). Individuals affected with BHD are characterized by BHD gene germline mutation. Reduced from ×20 (*upper and center right*) and ×40 (*lower right*). From Linehan *et al.* (3).

growth factor (EGF), and platelet-derived growth factor. Approaches have been developed to target the VEGF receptor with VEGF receptor-specific kinase inhibitors. Approaches have been developed to target VEGF itself with neutralizing antibodies. Agents such as ZD1839 (gefitinib) have been developed that target the tyrosine kinase activity of the EGF receptor (41). Combination agents such as ZD6474 that can inhibit at least two arms of the downstream HIF pathway, VEGF receptor and EGF receptor, are currently being evaluated in clinical trials (42).

TARGETING THE *c-Met* PATHWAY

Understanding the *c-Met* pathway provides opportunity for the development of disease-specific therapy for patients affected with type 1 papillary renal carcinoma. The germ-line mutations in *c-Met*, found in HPRC, cause constitutive receptor kinase activation (24, 43). *c-Met*, the cell surface receptor for hepatocyte growth factor (HGF), normally stimulates mitogenesis, migration (motogenesis), and morphogenesis in a wide range of cell types (44). On stimulation with HGF, the c-Met receptor kinase undergoes autophosphorylation on multiple tyrosine residues, two of which (Tyr^{1349} and Tyr^{1356}) form a binding site for several signal transducers, including phosphatidylinositol 3′-kinase, phospholipase C-γ, Src, Shp-2 phosphatase, signal transducers and activators of transcription 3, and the adapter proteins Crk, Grb2, Shc, and Gab1 (reviewed in ref. 45), among others. Gab1 also associates directly with activated c-Met via a distinct c-Met binding domain (46). Downstream HGF mitogenic signaling involves the Ras/MEK/extracellular signal-regulated kinase pathway; motogenic signaling involves Rac, Rho, Rho kinase, PAK, and cdc42 regulation of the actin cytoskeleton; cell dissociation involves junctional proteins such as β-catenin and E-cadherin; and cell adhesion involves focal adhesion kinase and associated focal adhesion components (45). The latter proteins also mediate HGF-induced cell shape changes and, with metalloproteinases, plasminogens, and their associated inhibitors, extracellular matrix invasion and branching morphogenesis. This HGF-regulated program of cell dissociation and increased cell motility coupled with increased protease production closely resembles the initial events of tumor metastasis *in vivo* (45).

Studies of the activating point mutations in c-Met found in type 1 papillary RCC suggest at least three strategies for therapeutic development: (*a*) block kinase activation with small molecule inhibitors of ATP binding; (*b*) block HGF-Met interaction; and (*c*) block interactions between activated c-Met and downstream intracellular signaling molecules. The potential therapeutic efficacy of blocking downstream signaling is supported by the observation that peptide mimetics of the c-Met sequence motif containing Tyr^{1356} inhibit invasive cell growth and transformation.

A potential strategy targeting intracellular effectors of c-Met receptor binding to Tyr^{1356} is based on the use of Src homology 2 domain antagonists. Atabey *et al.* (47) have evaluated the effects of several synthetic tripeptide-based inhibitors of the Grb2 Src homology 2 domain on HGF-stimulated mitogenesis, motogenesis, and extracellular matrix invasion. Grb2 binding is thought to be a critical link between HGF-stimulated c-Met activation and the activation of Rho, Ras, and Rac (48) in malignant transformation (49). These compounds potently block HGF-stimulated cell motility, matrix invasion, and branching morphogenesis with low nanomolar ED_{50} values. The compounds have shown no evidence of toxicity or loss of contractility required for cellular functions other than locomotion and invasion, further supporting their therapeutic potential as anti-

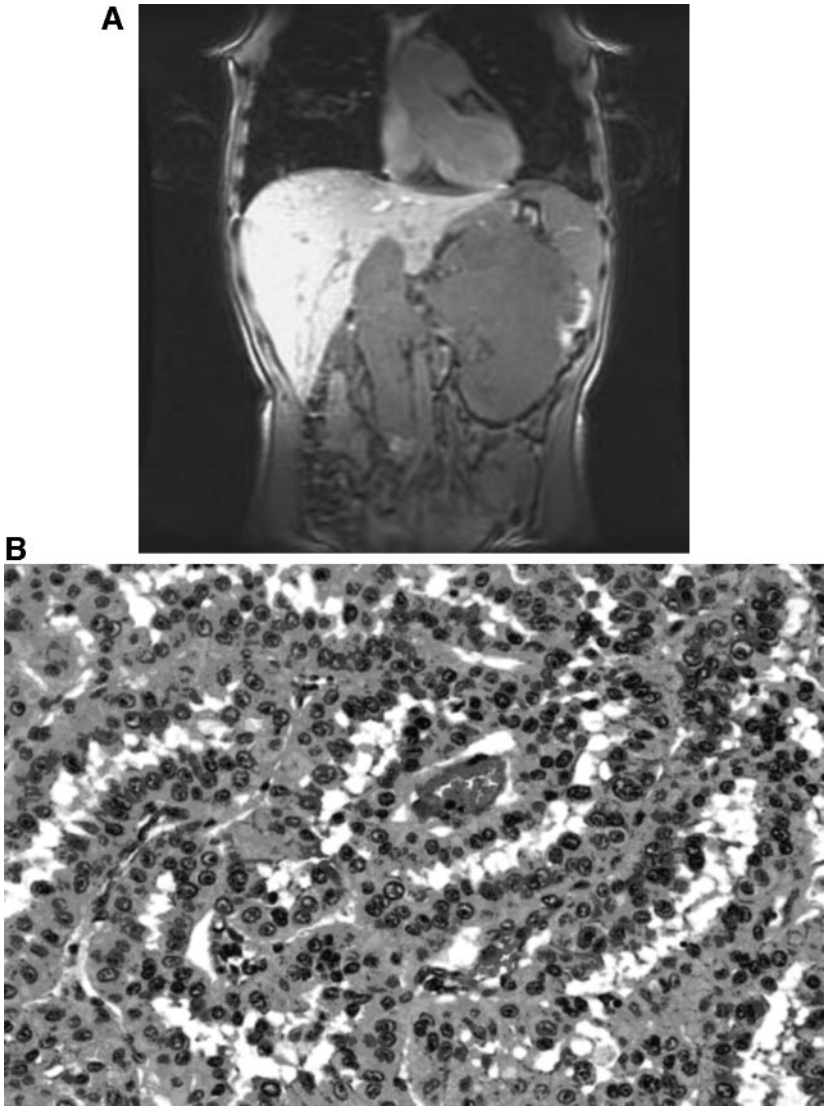

Fig. 5 HLRCC is a hereditary cancer syndrome (56) in which affected individuals are at risk for the development of an aggressive form of type 2 papillary renal carcinoma. HLRCC is characterized by germ-line mutation of the Krebs cycle enzyme, FH (33, 34). *A* shows an abdominal image of a young man affected with HLRCC with a large left-sided kidney mass that was found to by type 2 papillary RCC (*B*).

metastatic drugs for HPRC and other cancers in which the HGF signaling pathway is active.

HEAT SHOCK PROTEIN 90 AS A MOLECULAR TARGET IN RENAL CANCER

Although identification of novel therapeutic agents via molecular targeting offers the promise of great specificity for kidney cancer gene pathways coupled with reduced systemic toxicity, effective specific inhibition of individual proteins or signaling pathways in renal cancer may be subverted by the inherent genetic plasticity of cancer cells. An alternate approach is to target the basic machinery that allows renal cancer cells to adapt so successfully to their environment.

Molecular chaperones (also known as heat shock proteins because they were first observed in cells exposed to elevated temperature) assist general protein folding and prevent nonfunctional side reactions, such as the nonspecific aggregation of misfolded or unfolded proteins. Within the last decade, one chaperone in particular, heat shock protein 90 (Hsp90), has emerged as being important to the survival of cancer cells. A small molecule inhibitor of Hsp90, the benzoquinone ansamycin 17-allylamino-17-desmethoxygeldanamycin, has shown antitumor activity in several human xenograft models and is currently in clinical trials both as a single agent and in combination with other therapeutics (Fig. 6*A*−*C*).

Hsp90 in tumor cells forms the basis of a multichaperone complex that serves to stabilize and promote the activity of a limited number of "client" proteins. The Hsp90 inhibitor 17-allylamino-17-desmethoxygeldanamycin disrupts the function of this multichaperone complex, resulting in rapid inactivation of the client signaling protein followed by its chaperone- and ubiquitination-dependent degradation by the proteasome.

Hsp90 client proteins increased in renal cancer include HIF-1α and the receptor tyrosine kinases Met and KIT. HIF

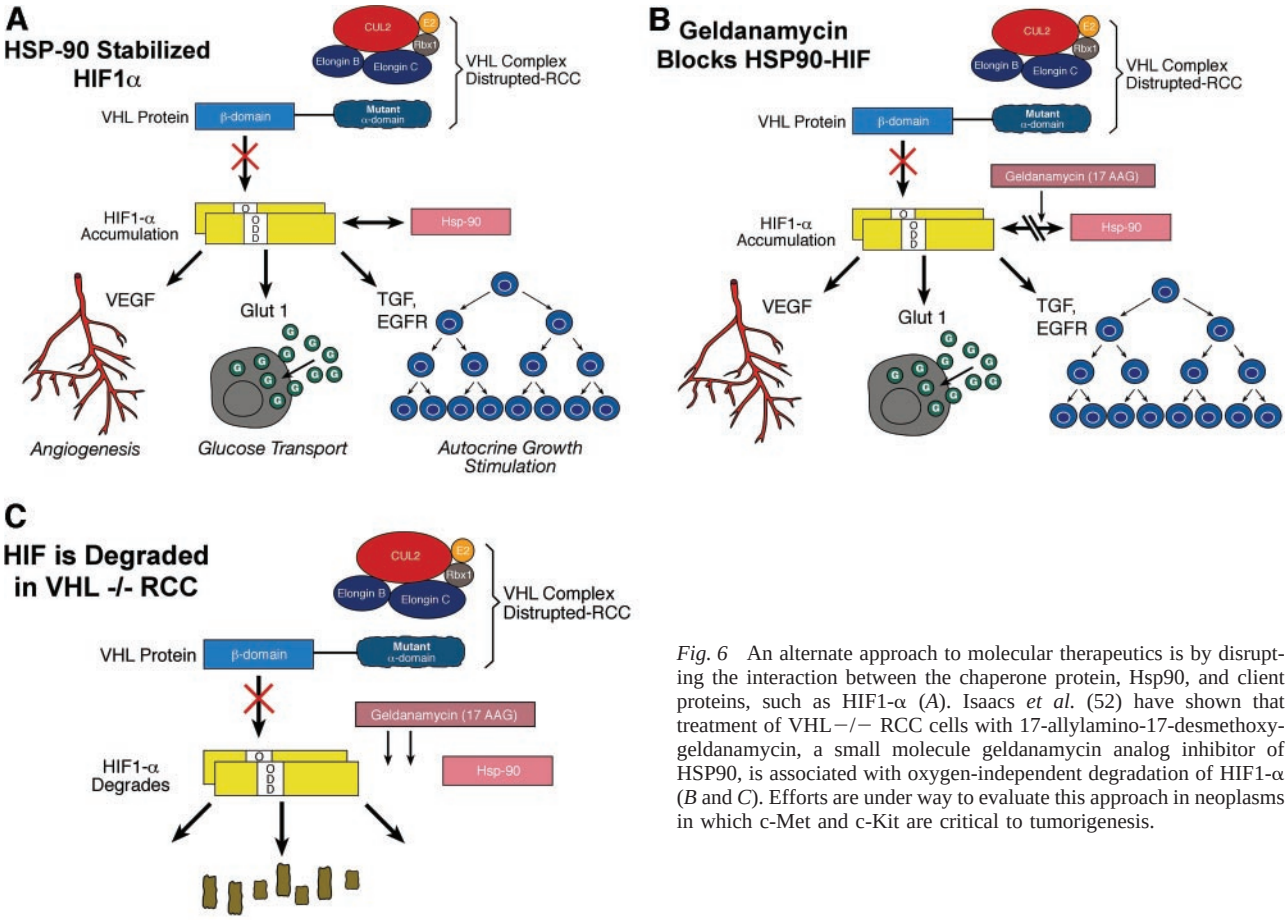

Fig. 6 An alternate approach to molecular therapeutics is by disrupting the interaction between the chaperone protein, Hsp90, and client proteins, such as HIF1-α (*A*). Isaacs *et al.* (52) have shown that treatment of VHL−/− RCC cells with 17-allylamino-17-desmethoxy-geldanamycin, a small molecule geldanamycin analog inhibitor of HSP90, is associated with oxygen-independent degradation of HIF1-α (*B* and *C*). Efforts are under way to evaluate this approach in neoplasms in which c-Met and c-Kit are critical to tumorigenesis.

interacts with Hsp90 (50), and Hsp90 inhibitors reduce HIF-dependent transcriptional activity (51–53). Hsp90 inhibition also down-regulates HIF protein expression by stimulating the protein's VHL- and oxygen-independent proteasomal degradation (52), suggesting the potential benefit of Hsp90 inhibitors in clear cell renal carcinoma.

KIT receptor tyrosine kinase is overexpressed in chromophobe and papillary RCCs (32, 54). KIT is also a Hsp90 client that is rapidly inactivated and destabilized in response to Hsp90 inhibition. Importantly, downstream signaling pathways normally stimulated by activated KIT, including the signal transducers and activators of transcription, AKT, and mitogen-activated protein kinase pathways, are also rapidly inhibited. Furthermore, AKT and RAF proteins are themselves Hsp90 clients and thus are also inactivated and destabilized in the presence of Hsp90 inhibitors. Finally, c-Met receptor tyrosine kinase, an important mediator of tumor cell motility and metastasis, also depends on Hsp90 for its activity and stability. Notably, c-Met is positively regulated by hypoxia via the HIF-1 pathway, and c-Met induction in tumors has been observed *in vivo* in response to angiogenesis inhibitors. Because Hsp90 is a shared requirement of both HIF-1α and c-Met, combining an inhibitor of Hsp90 with an antiangiogenic agent would be of potential interest.

SUMMARY

In summary, kidney cancer is not a single disease; it is made up of a number of different types of cancer that occur in the kidney, with different histologic types and different clinical courses, each responding differently to therapy and associated with alteration of different genes. Understanding the pathways of the genes that cause kidney cancer provides a unique opportunity for the development of disease-specific therapy for patients with advanced forms of this disease.

OPEN DISCUSSION

Dr. Robert Figlin: As we design clinical trials, should we start to categorize eligibility based on the genetics? For example, should we no longer be doing trials in clear cell carcinoma of the kidney but only trials in mutated VHL patients or wild-type patients?

Dr. W. Marston Linehan: We should pay attention to that. If you know whether the tumor has a *VHL* mutation, that could potentially tell you a lot about response to therapy. For example, if you have 100 patients treated with an agent that you predict would hit the VHL pathway, and the presence of a *VHL* mutation was documented in a large percentage of pathology specimens, wouldn't that make the trial a lot stronger?

Dr. Michael Gordon: We're on the cusp of segmenting out populations based on the target present, and we're struggling with the question, "What exactly is the target, and how can we define it?" I think the important question is, "How can we systematically look at it?" Even if we created a global effort to do this, we would still need the technology to reproducibly assess the target, and we would have to characterize the response before we could hone in on the issue of whether we could segment the population for a particular therapy.

Dr. Figlin: The problem with that is we may actually miss very effective agents for some subsets of populations where the activity may be quite impressive. One of the questions I would like to address is, "How do we enrich our populations to help the current trials achieve their greatest potential?"

Dr. Gordon: That becomes an issue of standardizing how we look at patients. What we are seeing is reproducible 10% to 15% response rates, and we don't know if it's the same patients or if we're missing high response rates in subgroups as we move through each drug.

Dr. Linehan: To characterize them all of the same way would be a start. For example, if you had an agent that hits the VHL-HIF pathway, it would be important to know the status of the pathway involved. A number of renal tumors besides clear cell kidney cancer highly express HIF-1 or HIF-2, so the more you characterize the pathway in an individual tumor, the better you will be able to evaluate response to a specific agent.

Dr. Janice Dutcher: Have you looked at people with sporadic tumors that have mixed histology? Some clear cell tumors have areas with non-clear cell features. Is the *VHL* mutation present in all of the tissue?

Dr. Linehan: We have learned to work closely with our pathologist. When she tells us it is clear cell with papillary features, those would be ones in which we would expect to see VHL mutations. On the other hand, if she says it is papillary with some clear cell features, we did not see the VHL mutation.

Dr. Michael Atkins: There is a lot of variability in how pathologists interpret those types of specimens. It's not always obvious how a clear cell tumor with papillary features differs from a papillary tumor with clear cell features. It sounds as if there may be more than just the one mutation in these cancers as they evolve. I believe you commented on the role of the *MET* gene in VHL syndrome and sporadic *VHL* mutated renal cancer. Did you mean to imply that the *MET* gene may play a role in this cancer as well? That the MET pathway may account for some of these papillary features seen in clear cell renal carcinomas?

Dr. Linehan: We think that strategies that target the *MET* pathway have relevance for clear cell kidney cancer as well.

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