Renal-Cell Carcinoma
Herbert T. Cohen, M.D., and Francis J. McGovern, M.D.

The classic presentation of renal-cell carcinoma includes the triad of flank pain, hematuria, and a palpable abdominal mass. Few patients now present in this manner. Roughly half the cases are now detected because a renal mass is incidentally identified on radiographic examination. Other common presenting features may be nonspecific, such as fatigue, weight loss, or anemia. Risk factors for renal-cell carcinoma include smoking, obesity, and hypertension, as well as acquired cystic kidney disease associated with end-stage renal disease. A 1.6:1.0 male predominance exists, and the peak incidence is in the sixth and seventh decades. Gross or microscopic hematuria is an important clinical clue to the diagnosis of renal-cell carcinoma; thus, hematuria should be evaluated promptly by a computed tomographic (CT) scan of the genitourinary tract and, in patients older than 40 years of age, by cystoscopy to rule out bladder cancer. Prognosis is closely related to the stage of disease (Fig. 1). The Heidelberg classification of renal tumors was introduced in 1997 as a means of more completely correlating the histopathological features with the identified genetic defects (Table 1).
the cases of sporadic clear-cell renal-cell carcinoma,\textsuperscript{8} which represents a major portion of all cases of renal-cell carcinoma.

VHL protein, the product of the \textit{VHL} gene, functions as a tumor suppressor, inhibiting growth when reintroduced into cultures of renal-cell carcinoma.\textsuperscript{9,10} Hypoxia-inducible genes are normally inhibited by VHL protein,\textsuperscript{11} including several encoding proteins involved in angiogenesis (e.g., vascular endothelial growth factor [VEGF]), cell growth (e.g., transforming growth factor \(\alpha\) [TGF-\(\alpha\)]), glucose uptake (e.g., the GLUT-1 glucose transporter), and acid–base balance (e.g., carbonic anhydrase IX [CA9]). When VHL protein is lost, these proteins are overexpressed, creating a microenvironment favorable for epithelial-cell proliferation (Fig. 4A). Thus, cells deficient in VHL protein behave as if they are hypoxic, even in conditions of normoxia. VHL protein, with elongin proteins C and B, binds cul2 protein (a member of the cullin family of ubiquitin ligase proteins), indicating that some VHL protein serves as the receptor subunit of a ubiquitin ligase complex that promotes the ubiquitination and destruction of proteins (Fig. 4B).\textsuperscript{12,13} VHL protein binds the transcriptional activators hypoxia-inducible factor 1\(\alpha\) (HIF-1\(\alpha\)) and 2\(\alpha\) (HIF-2\(\alpha\)) directly and destabilizes them.\textsuperscript{14} Furthermore, VHL protein promotes the ubiquitination and destruction of HIF-\(\alpha\).\textsuperscript{15-17} These VHL-regulated pathways are being studied as potential targets of therapies for clear-cell renal-cell carcinoma.

HIF is the key regulator of the hypoxic response in multicellular organisms. Thus, VHL protein has a central role in oxygen sensing. For HIF-\(\alpha\) to bind VHL protein, a proline residue must undergo hydroxylation, which is an unusual protein modification\textsuperscript{18,19} (Fig. 4B). A family of proline hydroxylases operates on HIF-\(\alpha\) in a graded fashion, so that the extent of hydroxylation depends on oxygen tension.\textsuperscript{20,21} Hydroxylation of an asparagine residue blocks the interaction of HIF-\(\alpha\) with the transcriptional coactivator p300.\textsuperscript{22} Thus, multiple hydroxylation steps cooperate to inhibit HIF-\(\alpha\) activity.

To correlate the genotype with the disease phe-
notype, naturally occurring \(\text{VHL}\) mutations have been evaluated to determine their effect on HIF-\(\alpha\) ubiquitination. An intriguing finding is that the \(\text{VHL}\) mutations that disrupt HIF-\(\alpha\) processing are the same as those associated with the vascular manifestations of von Hippel–Lindau disease, such as hemangioblastoma (Fig. 2).\(^{15,16,23,24}\) Since renal-cell carcinoma develops in only a subgroup of patients with hemangioblastoma, the overexpression of HIF-\(\alpha\) appears to be necessary for, but not sufficient to induce, renal tumorigenesis. Nevertheless, HIF-\(\alpha\) is vitally important to the pathogenesis of this disease. VHL-induced inhibition of HIF-\(\alpha\) is sufficient to suppress the growth of clear-cell renal-cell carcinoma in preclinical models.\(^{25,26}\) The cell-matrix protein fibronectin,\(^{27}\) chaperonin TRiC/ CCT,\(^{28}\) microtubules,\(^{29}\) and transcription factor Jade-1\(^{30-32}\) are all molecules that interact with VHL protein in a manner that is dependent on \(\text{VHL}\) mutation, suggesting that they may also contribute to disease pathogenesis.

Distinct from von Hippel–Lindau disease, familial clear-cell renal cancer has been reported in patients with translocations of chromosome 3p at a fragile site at 3p14.\(^{33}\) Loss of the translocated chromosome 3p probably implicates VHL protein in the development of these tumors. Additional translocations of chromosome 3 have been associated with clear-cell renal-cell carcinoma as well.

### Papillary Renal-Cell Carcinoma

Sporadic papillary renal-cell carcinoma has a five-year survival rate approaching 90 percent and a striking 5:1 male predominance. Localized papillary renal-cell carcinoma metastasizes less frequently than clear-cell renal-cell carcinoma.\(^{34}\) However, the survival rate for metastatic papillary renal-cell carcinoma is probably worse than that for clear-cell renal-cell carcinoma.\(^{35}\) The risk of both types is particularly increased among patients with end-stage renal disease. Chromosome 7, which harbors the \(\text{MET}\) proto-oncogene, is duplicated in 75 percent of sporadic papillary cases. There are two subtypes of papillary renal-cell carcinoma.\(^{36}\) Type 1 tumors are papillary lesions covered by small cells with pale cytoplasm and small oval nuclei with indistinct nucleoli, and type 2 tumors are papillary lesions covered by large cells with abundant eosinophilic cytoplasm. Type 2 cells are typified by pseudostratification and large, spherical nuclei with distinct nucleoli. Type 2 tumors are genetically more heterogeneous, have a poorer prognosis, and may arise from type 1 tumors.\(^{37}\) Papillary renal-cell carcinoma occurs in several familial syndromes (MIM number 605074). Hereditary papillary renal carcinoma is an autosomal dominant disorder associated with multifocal papillary renal-cell carcinoma\(^{38}\) with type 1 histologic features (Fig. 3).\(^{39}\) The causative gene, mutations in which are responsible for hereditary papillary renal carcinoma, has been identified at chromosome 7 and encodes \(\text{MET}\), a receptor tyrosine kinase that is normally activated by hepatocyte growth factor\(^{40}\) (Fig. 4C). In hereditary papillary renal carcinoma, the \(\text{MET}\) receptor tyrosine kinase domain undergoes autoactivating \(\text{amino-acid–substitut-}\

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### Table 1. Sporadic and Hereditary Renal-Cell Carcinomas and Genetic Defects According to Histologic Appearance.\(^*\)

<table>
<thead>
<tr>
<th>Sporadic Renal-Cell Carcinomas</th>
<th>Renal-Cell Carcinomas in an Inherited Syndrome</th>
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<tr>
<td><strong>Histologic Appearance</strong></td>
<td><strong>Gene and Frequency</strong></td>
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<tr>
<td>Conventional</td>
<td>75 VHL, 60</td>
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<tr>
<td>Papillary</td>
<td>12 MET, 13 TFE3, &lt;1</td>
</tr>
<tr>
<td>Chromophobe</td>
<td>4 Birt–Hogg–Dubé syndrome</td>
</tr>
<tr>
<td>Oncocytoma</td>
<td>4 Birt–Hogg–Dubé syndrome</td>
</tr>
<tr>
<td>Collecting duct</td>
<td>&lt;1</td>
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<tr>
<td>Unclassified</td>
<td>3–5</td>
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</table>

\(^*\) VHL denotes von Hippel–Lindau, FCRC familial clear-cell renal cancer, SDHB succinate dehydrogenase B, HPRC hereditary papillary renal carcinoma, HLRCC hereditary leiomyomatosis and renal-cell cancer, and \(\text{FH}\) fumarate hydratase.

\(^†\) Additional rare syndromes or infrequent associations are not included.
tion mutations, which promote cellular transformation.\textsuperscript{41} Subsequently, chromosome 7 harboring the MET mutation is duplicated, increasing the gene dose.\textsuperscript{42,43} Only a small percentage of the cases of the sporadic papillary type have MET mutations.\textsuperscript{40} Thus, the pathogenesis of hereditary papillary renal carcinoma is usually different from that of sporadic papillary renal-cell carcinoma.

Patients with the hereditary leiomyomatosis and renal-cell cancer syndrome (MIM number 605839) are at risk for cutaneous and uterine leiomyomas and solitary papillary renal-cell carcinoma with type 2 histologic features.\textsuperscript{44} Occasionally, cases of collecting-duct or clear-cell renal-cell carcinoma occur. These cases of papillary renal-cell carcinoma metastasize early and are the most aggressive of the familial types.\textsuperscript{45} Intriguingly, FH, the gene that causes this autosomal dominant syndrome, encodes fumarate hydratase, a Krebs-cycle enzyme.\textsuperscript{46} As with the loss of a tumor-suppressor gene, the wild-type FH allele is lost in hereditary leiomyomatosis and in lesions of renal-cell carcinoma.\textsuperscript{47} Along similar lines, cases of renal-cell carcinoma with solid histologic features or cases of the clear-cell form.
In contrast to sporadic renal-cell carcinoma (Panels A and C), fewer steps are required for the development of renal-cell carcinoma in the inherited forms of the disease (Panels B and D), because all of the patient’s cells have a mutation that predisposes the patient to the disease. As a result, the disease associated with the familial syndromes occurs earlier and is often multifocal. Each familial renal cancer syndrome is autosomal dominant. In von Hippel–Lindau disease, a cellular recessive mechanism is involved, since both copies of the \( VHL \) gene are inactivated (Panels A and B). \( VHL \) is a classic tumor-suppressor gene. In hereditary papillary renal carcinoma, one copy of the \( MET \) gene has an activating mutation, which is inherited (Panel D). Chromosome 7, which includes the defective \( MET \) allele, becomes duplicated, increasing the level of expression of the activated \( MET \) protein, which is a receptor tyrosine kinase for hepatocyte growth factor. Activated \( MET \) is a classic oncogene. A plus sign represents the wild-type allele; a minus sign represents a null allele. A plus sign in red type represents a mutated, activated allele; two plus signs in red type represent duplication of that allele.

**Figure 3. Steps in the Development of Renal-Cell Carcinoma.**

In contrast to sporadic renal-cell carcinoma (Panels A and C), fewer steps are required for the development of renal-cell carcinoma in the inherited forms of the disease (Panels B and D), because all of the patient’s cells have a mutation that predisposes the patient to the disease. As a result, the disease associated with the familial syndromes occurs earlier and is often multifocal. Each familial renal cancer syndrome is autosomal dominant. In von Hippel–Lindau disease, a cellular recessive mechanism is involved, since both copies of the \( VHL \) gene are inactivated (Panels A and B). \( VHL \) is a classic tumor-suppressor gene. In hereditary papillary renal carcinoma, one copy of the \( MET \) gene has an activating mutation, which is inherited (Panel D). Chromosome 7, which includes the defective \( MET \) allele, becomes duplicated, increasing the level of expression of the activated \( MET \) protein, which is a receptor tyrosine kinase for hepatocyte growth factor. Activated \( MET \) is a classic oncogene. A plus sign represents the wild-type allele; a minus sign represents a null allele. A plus sign in red type represents a mutated, activated allele; two plus signs in red type represent duplication of that allele.
have been reported in patients with the hereditary paraganglioma syndrome (MIM number 115310). Certain forms of hereditary paraganglioma are associated with germ-line defects in the succinate dehydrogenase B gene.48 Succinate dehydrogenase B protein is another mitochondrial, Krebs-cycle enzyme. Thus, an intriguing connection exists among cellular ATP production, the hypoxic response, and tumorigenesis in both neuronal and kidney tissue.

A number of sporadic cases of papillary renal-cell carcinoma have chromosomal translocations involving the TFE3 gene at chromosome Xp11.2.49-51 Children and young adults are affected without predilection for sex, and the histologic features of such cases have been variably described as papillary renal-cell carcinoma, clear-cell renal-cell carcinoma, or a unique type of pathology. The TFE3 gene encodes a helix–loop–helix transcription factor related to the proto-oncogene product c-myc. Key TFE3 domains become fused with other gene products, and renal-cell carcinoma is probably due to TFE3 overexpression.

**ONOCYTOMA AND CHROMOPHOBE RENAL-CELL CARCINOMA**

Oncocytomas, which are benign, account for about 4 percent of nephrectomies performed because renal-cell carcinoma is suspected. The chromophobe variant of renal-cell carcinoma also accounts for 4 percent of all cases of renal-cell carcinoma52 and may have a benign course after surgery, provided that the tumor stage and grade are favorable.53 Oncocytoma is thought to originate from type A intercalated cells of the collecting duct, whereas chromophobe renal-cell carcinoma is thought to originate from type B intercalated cells.

The Birt–Hogg–Dubé syndrome (MIM number 135150) is a rare autosomal dominant disorder characterized by hair-follicle hamartomas (fibrofolliculomas) of the face and neck.54-57 About 15 percent of affected patients have multiple renal tumors, most often chromophobe or mixed chromophobe–oncocytomas. Occasionally, papillary or clear-cell renal-cell carcinoma develops in patients with the Birt–Hogg–Dubé syndrome. BHD, the gene implicated in the syndrome, encodes the protein folliculin, a suspected tumor suppressor. BHD mutations occur only rarely in sporadic renal-cell carcinoma.59,60 The Birt–Hogg–Dubé renal phenotype supports the existence of a close relationship between oncocytoma and chromophobe renal-cell carcinoma.

**COLLECTING-DUCT RENAL-CELL CARCINOMA**

Collecting-duct renal-cell carcinoma accounts for less than 1 percent of all cases of renal-cell carcinoma and is typically an aggressive tumor. Medullary carcinoma of the kidney, which may be a variant of the collecting-duct type, is associated with sickle
cell trait or disease. The collecting-duct form may be most similar to transitional-cell carcinoma of the urothelium.

**MANAGEMENT OF SPORADIC AND HEREDITARY RENAL-CELL CARCINOMA**

An enhancing renal mass on a CT scan obtained after the administration of contrast material is a strong clue that renal cancer is present. A staging workup should be performed before treatment is initiated. Multiple enhancing lesions, or a family history of renal-cell carcinoma, particularly in persons younger than 50 years of age, suggests a hereditary predisposition to the disease. Von Hippel–Lindau disease, hereditary leiomyomatosis and renal-cell cancer, and the Birt–Hogg–Dubé syndrome all have extrarenal manifestations, whereas familial clear-cell renal cancer and hereditary papillary renal carcinoma do not. Thus, a careful physical examination including ophthalmologic, neurologic, and dermatologic evaluation may be helpful. CT scanning or magnetic resonance imaging (MRI) of the abdomen and pelvis may reveal uterine tumors in patients with hereditary leiomyomatosis and renal-cell cancer or renal cysts or pancreatic or adrenal involvement in patients with von Hippel–Lindau disease.

Patients with hereditary renal-cell carcinoma should be closely monitored. CT before and after the administration of contrast material is the best test for detection and assessment of renal masses, with gadolinium-enhanced MRI as an alternative. Such studies can be performed at intervals ranging from every three to six months to every two to three years, depending on the size of the lesions and the type of syndrome. Larger masses require more frequent evaluation. Because small masses are usually of low grade, they can be observed until they reach 3 cm, at which time they should be removed. However, tumors caused by hereditary leiomyomatosis and renal-cell cancer should be excised immediately because of their aggressive nature. Patients with von Hippel–Lindau disease should undergo MRI studies of the brain and spinal cord to screen for hemangioblastoma. A family pedigree should be generated, and family members at risk should be encouraged to seek medical attention. Testing is available for the VHL, MET, FH, and BHD genes. One goal of such testing is to free unaffected family members from continued cancer screening. Organizations such as the VHL Family Alliance (www.vhl.org) are a vital resource for patients, families, physicians, and researchers.

**PROGNOSIS**

Defining the prognosis of renal-cell carcinoma is important for both therapeutic decision-making and counseling patients. For metastatic renal-cell carcinoma, poor prognostic factors include a low Karnofsky performance-status score (a standard way of measuring functional impairment in patients with cancer), a high level of serum lactate dehydrogenase, a low hemoglobin level, and a high corrected level of serum calcium. The University of California, Los Angeles, Integrated Staging System was developed to evaluate the prognosis at diagnosis and in the presence of metastatic disease; it includes tumor–node–metastasis (TNM) staging, the patient’s score on the Eastern Cooperative Oncology Group performance-status scale (another measure of functional impairment in patients with cancer), and the Fuhrman nuclear grade, which assesses histologic features of the tumor. This system has been used successfully in more than 4000 patients at eight international centers.

**SURGICAL TREATMENT**

**RADICAL NEPHRECTOMY**

Surgical excision is the primary treatment for renal-cell carcinoma. Radical nephrectomy, which includes removal of the kidney en bloc with Gerota’s fascia, the ipsilateral adrenal gland, and regional lymph nodes, has been the standard therapy, although more limited approaches are being explored. The surgical approach is determined by the size and location of the tumor within the kidney, the TNM stage, and any special anatomical considerations.

Staging and evaluation for the presence of metastases, including a careful history-taking and physical examination, should be completed before surgery. Routine laboratory studies should include measurement of the hematocrit and serum levels of creatinine, calcium, and alkaline phosphatase and a urinalysis for proteinuria. Imaging studies, such as radiographs of the chest, CT of the abdomen and pelvis, and in some cases, MRI evaluation of the renal vein and inferior vena cava, CT of the chest or head, or bone scanning may be needed. The fre-
Frequency of follow-up after surgery depends on the stage of the tumor.

**Surgery for Metastatic Disease**

Nephrectomy may be warranted, even in the presence of metastatic disease. The combination of interferon alfa and nephrectomy is superior to interferon alfa alone, offering a survival advantage of 3 to 10 months. Surgical excision of a solitary metastasis in patients with advanced renal-cell carcinoma is recommended in many cases, but this approach has not yet been proved to be effective in prolonging survival.

**Nephron-Sparing Partial Nephrectomy**

Nephron-sparing partial nephrectomy has gained acceptance for treating tumors less than 4 cm in diameter. Other indications for partial nephrectomy may include a solitary kidney, bilateral renal masses, or renal insufficiency, as well as the presence of hypertension, diabetes, or hereditary renal-cell carcinoma syndromes. Results achieved with nephron-sparing surgery are similar to those with radical nephrectomy, but a disadvantage is a rate of local recurrence of 3 to 6 percent.

**Laparoscopic Nephrectomy**

First reported in 1991, laparoscopic nephrectomy has accelerated the evolution toward minimally invasive surgical management of renal-cell carcinoma. The benefits of the laparoscopic approach include decreased postoperative pain, a shorter hospitalization, and a quicker recovery. The laparoscopic approach has been used for both radical nephrectomy and partial nephrectomy. The laparoscopic partial nephrectomy, however, is a technically demanding procedure with the potential for increased perioperative complications.

**Percutaneous Ablative Approaches**

The most recent evolution in the surgical management of small tumors has been percutaneous thermal ablative techniques that use radiofrequency heat ablation or cryoablation to destroy tumor cells. A needle probe is advanced through the skin and directed into the tumor under image guidance. Although early results of radiofrequency ablation and cryoablation are encouraging, larger trials with long-term follow-up are needed. The rates of complications appear to be low, but reported adverse events include intraoperative and postoperative hemorrhage, urinary leakage, and injury to adjacent structures. Because identification of the type of renal-cell carcinoma is important, a core biopsy of the renal mass should be performed as part of the procedure. Ideal candidates for minimally invasive percutaneous ablative therapy are patients with tumors less than 3 cm in diameter who have serious coexisting conditions and for whom standard approaches would pose substantial risks. Patients with multifocal tumors may also benefit from minimally invasive percutaneous procedures. High-frequency focused ultrasound applied externally to the body is being studied as another potential minimally invasive therapy.

**Medical Treatment**

Medical therapies are generally offered for locally advanced or metastatic renal-cell carcinoma (Table 2), and much of the clinical experience with this approach is in patients with the clear-cell type. Because response rates are low, the need to identify new therapeutic agents is great.

**Chemotherapy**

Rates of response to chemotherapy alone are low (roughly 4 to 6 percent). Drug resistance may be related to the expression of the multidrug resistance transporter in proximal-tubule cells — the cells from which clear-cell and papillary renal-cell carcinoma may originate. Chemotherapy may be more efficacious for advanced non–clear-cell renal-cell carcinoma, particularly the collecting-duct type. A phase 2 trial of carboplatin and paclitaxel for the collecting-duct form of the disease is under way.

**Immunomodulatory Therapies**

The value of immunomodulatory therapy for clear-cell renal-cell carcinoma is supported by reports of occasional spontaneous tumor regression, infrequent complete regression of metastatic disease with cytokine therapies, and promising early results with allogeneic stem-cell transplantation and tumor vaccines. The goal of immunomodulatory therapy is to boost either tumor antigenicity or host surveillance. Unique tumor antigens may also be inducible in renal-cell carcinoma.

*Interferon Alfa*

About 14 percent of cases of metastatic clear-cell renal carcinoma respond to interferon alfa alone. Various doses and routes have been used.
The median duration of response is six months and rarely exceeds two years. Because the side effects of the drug are not onerous, it appears to be a good choice to use in combination with other agents in experimental approaches.

Interleukin-2

High-dose interleukin-2 is the standard therapy for advanced renal-cell carcinoma and is the only regimen for this disease approved by the Food and Drug Administration. However, many patients with metastatic disease cannot take high-dose interleukin-2, because it causes a capillary leak syndrome or because it is not available in all treatment centers. High-dose interleukin-2 induces responses in 21 percent of patients, as compared with only 13 percent of patients who receive low-dose interleukin-2. The median duration of response has been reported to be 54 months overall, and for those with a complete response, the median duration of a response is yet to be reached. Interleukin-2 has also been used in combination with other drugs, but it is unclear whether combined therapy achieves better results than interleukin-2 alone. Thus, interleukin-2 is a highly effective therapy for a subgroup of patients with metastatic disease. Identifying features predictive of a response to interleukin-2 would represent a further advance, and efforts are being made to identify patients with clear-cell renal carcinoma who would be likely to have a response to interleukin-2 therapy on the basis of pathological characteristics and expression of CA9.

Adjuvant Therapy

Given the high rate of recurrence of renal-cell carcinoma after nephrectomy, a follow-up adjuvant approach would be desirable, especially for patients with high-risk, locally advanced disease. However, conventional chemotherapy, interferon alfa, or even interleukin-2 has not proved effective as an adjuvant therapy. Approaches currently being tested include tumor vaccines and a monoclonal antibody directed against CA9.

Evolving Therapies

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<th>Table 2. Medical Therapies for Advanced Renal Cancer.</th>
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<td><strong>FDA-approved regimen</strong></td>
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<td>High-dose interleukin-2 (aldesleukin, immunomodulatory cytokine)</td>
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<td><strong>Commonly used agents</strong></td>
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<td>Low-dose interleukin-2</td>
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<tr>
<td>Interferon alfa (immunomodulatory cytokine)</td>
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<td><strong>Experimental therapies</strong></td>
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<td>Bevacizumab (humanized VEGF-neutralizing antibody)</td>
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<td>Sunitinib (VEGF receptor and multitargeted kinase inhibitor)</td>
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<td>Sorafenib tosylate (VEGF receptor and multitargeted kinase inhibitor)</td>
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<td>Panitumumab (human EGFR-neutralizing antibody)</td>
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<td>Gefitinib (EGFR tyrosine kinase inhibitor)</td>
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<td>Erlotinib (EGFR tyrosine kinase inhibitor)</td>
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<td>Temsirolimus (inhibitor of the mammalian target of rapamycin)</td>
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<tr>
<td>Tumor vaccines</td>
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<td>Allogeneic stem-cell transplantation</td>
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* FDA denotes Food and Drug Administration, VEGF vascular endothelial growth factor, and EGFR epidermal growth factor receptor. The trade name for interleukin-2 is Proleukin; for bevacizumab, Avastin; for sunitinib malate, Sutent; for sorafenib tosylate, Nexavar; for gefitinib, Iressa; for erlotinib, Tarceva.

Allogeneic stem-cell transplantation performed after the administration of a non–marrow ablative regimen elicits a potent graft-versus-tumor effect and appears promising for treating clear-cell renal-cell carcinoma. Protocols developed at the National Institutes of Health have used myelosuppressive pretreatment, followed by an infusion of donor CD34+ cells and T cells from an HLA-identical sibling. A course of immunosuppressive agents, such as cyclosporine, is used to limit graft-versus-host disease and is rapidly tapered. Twenty of the first 45 patients with metastatic renal-cell carcinoma who underwent stem-cell transplantation had a response (44 percent). However, results in some other centers have been less promising. The responses have correlated well with the development of graft-versus-host disease and with the conversion of T-cell chimerism to full donor origin. One goal is to identify the tumor epitopes that are initiating the graft-versus-tumor response to improve treatment specificity. The two drawbacks to stem-cell transplantation have been severe graft-versus-host disease, which can be life-threatening, and the need for a haplotype-matched sibling donor. Prognosis is also an important guide to patient selection, since responses take several months. The next generation of strategies for stem-cell transplantation may include the use of tumor vaccines after transplantation as well as the use of cytokine therapy to boost recipient or even donor immunity.
TUMOR VACCINES
Tumor vaccines represent a potential means of enhancing host immunity. A promising approach to the treatment of advanced clear-cell renal carcinoma uses autologous or donor dendritic cells, which initiate a primary immune response by presenting antigen in the context of costimulatory molecules. Dendritic cells can be pulsed with tumor protein, DNA, or RNA; they can even be fused with tumor cells to present tumor antigens in a context favorable for therapy. Such vaccines are generally well tolerated, but they will require further optimization. Concomitant administration of cytokines may improve the response to vaccines.

TARGET ANTIGENS
A goal of stem-cell or vaccine therapies is to characterize the tumor antigens involved in the immune response. One potential target is the G250 renal cancer antigen, which has been identified as CA9. The CA9 gene is a target of HIF and so is overexpressed in VHL-related clear-cell renal carcinoma, even in the earliest lesions of von Hippel–Lindau disease. Thus, in cases of renal-cell carcinoma, a high proportion of CA9-positive cells may be associated with a more favorable prognosis. As a transmembrane protein, CA9 may also be a therapeutically useful tumor antigen. It will be important to identify additional target antigens.

THERAPIES TARGETING VEGF AND TGF-α PATHWAYS
Originally identified as regulated by VHL, VEGF and TGF-α are now promising therapeutic targets in clear-cell renal carcinoma. The manner in which these molecules interact with the cancer epithelium and surrounding vascular endothelium leads to tumor progression (Fig. 4A). A combination of therapies based on rational targets such as these may therefore be a powerful approach to advanced renal-cell carcinoma.

VEGF-Pathway Components as Molecular Targets
VEGF is overexpressed throughout clear-cell renal-cell carcinoma tissue and may be the most important tumor angiogenic factor. A randomized phase 2 trial involving patients with metastatic renal-cell carcinoma investigated the efficacy of bevacizumab, a humanized VEGF-neutralizing antibody. This agent extended the interval before tumor progression to 4.8 months, as compared with 2.5 months for placebo. Bevacizumab therefore provided a key “proof of principle” of the efficacy of anti-angiogenic therapy and may offer additional benefit when given in combination with other drugs. Inhibitors of VEGF receptor tyrosine kinase are being developed and tested. Indeed, the multi-targeted kinase inhibitors sunitinib and sorafenib have shown great promise in phase 2 and phase 3 trials, with at least stabilization of disease in as many as 70 percent of patients with cytokine-refractory disease.

TGF-α—Pathway Components as Molecular Targets
TGF-α is a potent growth factor for epithelial cells that acts through the epidermal growth factor receptor (EGFR), which is a receptor tyrosine kinase. TGF-α is overexpressed in the epithelium in clear-cell renal carcinoma and is a VHL target. Overexpression of TGF-α is an early event in the pathogenesis of this disease. Furthermore, growth of renal cancer cells in culture is dependent on TGF-α. Thus, the TGF-α pathway is a logical choice for therapeutic intervention.

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Antibodies against EGFR are thought to bind EGFR and promote its down-regulation from the cell surface. A fully human monoclonal antibody against human EGFR, called panitumumab (ABX-EGF), has been evaluated in a phase 2 trial involving 88 patients with metastatic renal-cell carcinoma. Only one patient had a complete response, and two had partial responses—a disappointing result. Small-molecule inhibitors of the EGFR tyrosine kinase are also being developed. The quinazolines gefitinib and erlotinib are now in phase 2 trials. In a phase 1 trial of erlotinib, just one patient with metastatic disease had a complete response. The median survival rate was 15 months. The notable activity of the drug in patients with poor prognostic features prompted a phase 3 trial. Other options are being pursued, including agents targeting HIF.

Other Approaches
Temsirolimus (CCI-779), a selective inhibitor of the mammalian target of rapamycin, has shown efficacy in a phase 2 trial of metastatic renal-cell carcinoma. Temsirolimus may inhibit HIF as well. Partial responses were noted in 7 percent of patients, and minor responses in 26 percent. The median survival rate was 15 months. The notable activity of the drug in patients with poor prognostic features prompted a phase 3 trial. Other options are being pursued, including agents targeting HIF.
The mutative, activated hepatocyte growth factor receptor MET could be targeted in the papillary form of the disease. The immune responsiveness of renal-cell carcinoma provides an opportunity for the development and optimization of vaccines and other immune therapies. Preservation of as much renal function as possible and reduced rates of complications are two goals of new minimally invasive approaches to renal-cell carcinoma; other goals are to identify early markers of disease, prognosis, or responsiveness to therapy.

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REFERENCES


