

Understanding the Natural Biology of Kidney Cancer: Implications for Targeted Cancer Therapy

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During the past several decades, there has been a significant increase in the understanding of the biology, clinical behavior, and prognostic factors of renal cell carcinoma (RCC). Such progress has led to greater sophistication in the diagnosis and classification of RCC. Here, we review recent advances in our knowledge of the biologic characteristics of RCC that have resulted in notable achievements in staging, prognosis, patient selection, and treatment. [Rev Urol. 2007;9(2):47-56]

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The incidence of renal cell carcinoma (RCC) has been increasing steadily over the past decades. It is estimated that more than 38,000 Americans developed RCC in 2006, and more than 12,000 are expected to die from the disease.¹ The diagnostic trend is mainly due to the widespread use of noninvasive abdominal imaging procedures, which detect incidental renal lesions.² The majority of these incidentally detected tumors are at low stages and low

grades and are amenable to curative surgical treatments; therefore, they carry a good prognosis.^{3,4} However, a stable proportion of 20% to 30% of patients still present with metastatic disease, and 20% to 30% of the patients who undergo curative surgery will develop metastatic disease during follow-up.⁵ Despite the recent arrival

accurately recognized as a family of cancers in which each results from a distinct genetic abnormality with unique morphologic features, but all are derived from renal tubular epithelium.

In 1986, Thoenes and colleagues⁸ established what became known as the Mainz classification of renal tu-

Today, RCC is more accurately recognized as a family of cancers in which each results from a distinct genetic abnormality with unique morphologic features, but all are derived from renal tubular epithelium.

of targeted drugs, metastatic RCC remains an incurable condition for the majority of these patients.

RCC is a unique solid tumor that continues to intrigue basic and clinical scientists alike. In recent years, new discoveries and developments in genetics and molecular markers have led to a better understanding of the underlying pathways driving RCC biology and have subsequently led to new classifications and drugs that have had an impact on diagnosis, classification, patient selection, and therapy.⁶ The discovery of the von Hippel-Lindau (VHL) tumor suppressor gene and the hypoxia-induced pathway in clear cell RCC has provided a valuable substrate for the application of new strategies to diagnosis, patient selection, and targeted therapy.⁷ Herein, we review the strides in classification and underlying pathways in RCC.

Histology and Staging: From Tumor-Node-Metastasis to Integrated Staging

Categorizing tumors into subgroups with similar pathologic features may be helpful in understanding the disease, selecting therapy, and predicting prognosis. RCC is composed of various cell types and growth patterns. Historically, RCC was regarded as a single entity. Today, RCC is more

accurately recognized as a family of cancers in which each results from a distinct genetic abnormality with unique morphologic features, but all are derived from renal tubular epithelium. Based on their studies, the authors proposed a classification based on cell type and growth pattern that recognized clear cell, chromophilic, chromophobe, spindle-shaped, oncocytic, and unclassified tumor cell types, and solid, tubulopapillary, and mixed growth patterns. Throughout the 1990s, advances in the understanding of the genetic alterations underlying the pathogenesis of RCC reinforced the concept that the distinct subtypes of RCC each have their own associated genetic lesions. Under consideration of cytologic, growth pattern, and genetic features, the Union Internationale Contre le Cancer (UICC) and the American Joint Committee on Cancer (AJCC) introduced a new classification in 1997 that distinguishes clear cell, papillary, chromophobe, collecting duct, and unclassified RCC.⁹ These differences reflect a greater sophistication in tumor analysis based on cytology, histology, genetic aberrations, glycogen content, electron microscopy of cytoplasmic microvesicles, and immunohistochemistry of intermediate filament proteins, which strongly suggest that these subtypes in fact arose in distinct regions of the renal tubule despite their basic cytoplasmic staining properties. Their proposed classification is summarized in Table 1.

These histologic subtypes are associated with distinct genetic alterations. Principally, changes in the genes can be “loss-of-function” mutations in tumor suppressor genes and “gain-of-function” mutations in proto-oncogenes, which are then called oncogenes. Research regarding heredity of clear cell RCC has led to the identification of the relevant gene locus on the short arm of chromosome 3.¹⁰⁻¹² Additionally, these aberrations have been found in nonhereditary, sporadic clear cell RCC. This loss-of-function mutation led to the assumption of the existence of a tumor suppressor gene, and subsequent research led to the identification of the VHL gene.¹³ In papillary RCC, trisomies of chromosomes 7 and 17 and a loss of chromosome Y are typical findings.¹⁴⁻¹⁷ Occurrence of a

Table 1
Current Classification of Renal Cell Tumors and Frequency in a Surgical Series of 1600 Consecutive Patients With Renal Cell Tumor at UCLA

Tumor	Percentage
Benign neoplasms	7
Papillary and metanephric adenoma	3
Oncocytoma	61
Angiomyolipoma	29
Other	7
Malignant neoplasms	93
Clear cell renal carcinoma	82
Papillary renal carcinoma	11
Chromophobe renal carcinoma	5
Collecting duct carcinoma	<1
Renal cell carcinoma, unclassified	2

relevant trisomy is usually associated with activation of a proto-oncogene, which is then called a gain-of-function mutation. Finally, the *MET* proto-oncogene on chromosome 7q was identified in hereditary papillary RCC.^{18,19} However, mutations in the *MET* proto-oncogene are found in only a small proportion of patients with sporadic papillary RCC. Launonen and associates²⁰ reported on a novel familial renal cancer syndrome called “hereditary leiomyomatosis and renal cell cancer,” which involves the *FH* gene encoding fumarate hydratase, an enzyme responsible for catalysis in the conversion of fumarate to malate. This syndrome is characterized by cutaneous and uterine leiomyomas and aggressive type 2 papillary RCC.^{20,21} Another familial RCC syndrome called Birt-Hogg-Dube syndrome has been described.²² This syndrome is a genodermatosis also characterized by an increased risk for multiple or bilateral RCC, particularly chromophobe RCC and renal oncocytomas.²³ Table 2 summarizes the most relevant chromosomal aberrations among clear cell, papillary, and chromophobe RCC.

Subtype	Typical Aberration
Clear cell	3p-
Papillary*	Trisomies (3q, 7, 12, 16, 17, 20)
Chromophobe	Monosomies (1, 2, 6, 10, 13, 17, 21)

*Overall, the number of chromosomal alterations appears to be larger in type 2 than in type 1 papillary renal cell carcinoma.⁸⁴
Data from Störkel S et al.⁹

Primary Tumor (T)	
T1a	Tumor 4 cm or less in greatest dimension, limited to the kidney
T1b	Tumor more than 4 cm but not more than 7 cm in greatest dimension, limited to the kidney
T2	Tumor more than 7 cm in greatest dimension, limited to the kidney
T3a	Tumor directly invades adrenal gland or perirenal and/or renal sinus fat but not beyond Gerota’s fascia
T3b	Tumor grossly extends into the renal vein or its segmental (muscle-containing) branches, or the vena cava below the diaphragm
T3c	Tumor grossly extends into the vena cava above the diaphragm or invades the wall of the vena cava
T4	Tumor invades beyond Gerota’s fascia
Regional Lymph Nodes (N)	
N0	No regional lymph node metastasis
N1	Metastasis in a single regional lymph node
N2	Metastasis in more than 1 regional lymph node
Distant Metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

From American Joint Committee on Cancer.²⁴

Staging of RCC is performed worldwide according to the tumor-node-metastasis (TNM) classification, which was most recently modified in 2002 (Table 3).²⁴ The main change was the subdivision of tumor stage T1 into T1a and T1b based on a tumor size cutoff of 4 cm. For tumor grading, several different staging systems exist.²⁵ The most frequently used system is the Fuhrman grading scheme, which distinguishes 4 grades.²⁶ Grade 1 carcinomas have round, uniform nuclei approximately 10 μm in diameter with minute or absent nuclei. In grade 2, the nuclei are slightly irregular, with diameters of approximately 15 μm and visible nucleoli on 400-fold magnification. The nuclei in grade 3 are moderately irregular, with diameters of at least 20 μm and large nucleoli visible on 100-fold magnifi-

cation. Grade 4 nuclei are markedly irregular and pleomorphic, with clumped chromatin. TNM stage and grade are considered to be the most important prognostic factors in RCC.^{27,28}

The clinical behavior of RCC, however, results from complex interactions among multiple factors. This realization has led to an increasing interest in using integrated staging systems to predict outcome by combining several prognostic variables. TNM stage, Fuhrman grade, and the patient’s performance status according to the Eastern Cooperative Oncology Group (ECOG) criteria²⁹ comprise the University of California Integrated Staging System (UISS), which originally stratified patients into 5 different categories.³⁰ The UISS was later modified into a

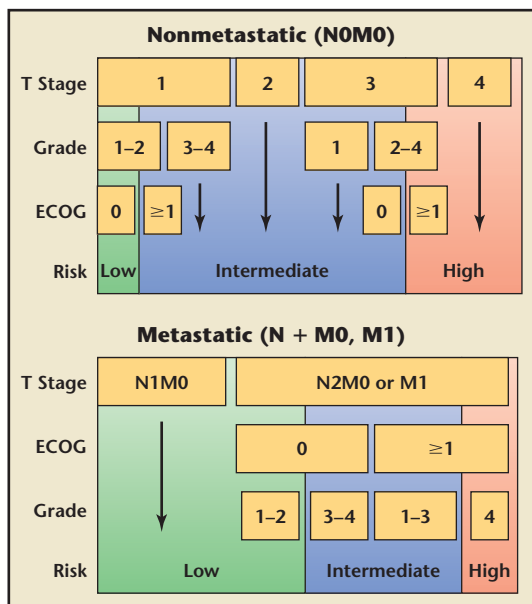


Figure 1. The University of California Integrated Staging System. ECOG, Eastern Cooperative Oncology Group. Data from Zisman A et al.⁵

simplified system containing 6 categories, 3 for nonmetastatic and 3 for metastatic disease (Figure 1).⁵ The UISS classifies patients into 3 different risk categories: low, intermediate, and high. An updated analysis of the UISS shows that the 2- and 5-year survival rates for these categories were 99% and 97% (nonmetastatic [NM] low risk), 93% and 81% (NM intermediate risk), 82% and 63% (NM high risk), 69% and 39% (metastatic [M] low risk), 37% and 17% (M intermediate risk), and 7% (M high risk) (Figure 2). This system permits the selection of high-risk patients most suitable for adjuvant treatment trials and the assignment of patients with metastatic disease to different therapeutic strategies. For example, patients in the metastatic high-risk group had a median survival of 6 months, which leads to the conclusion that the current treatment strategy consisting of nephrectomy and immunotherapy/angiogenesis-targeted therapy is ineffective. Hence, these patients might be better candidates for agents targeting the mammalian target of rapamycin

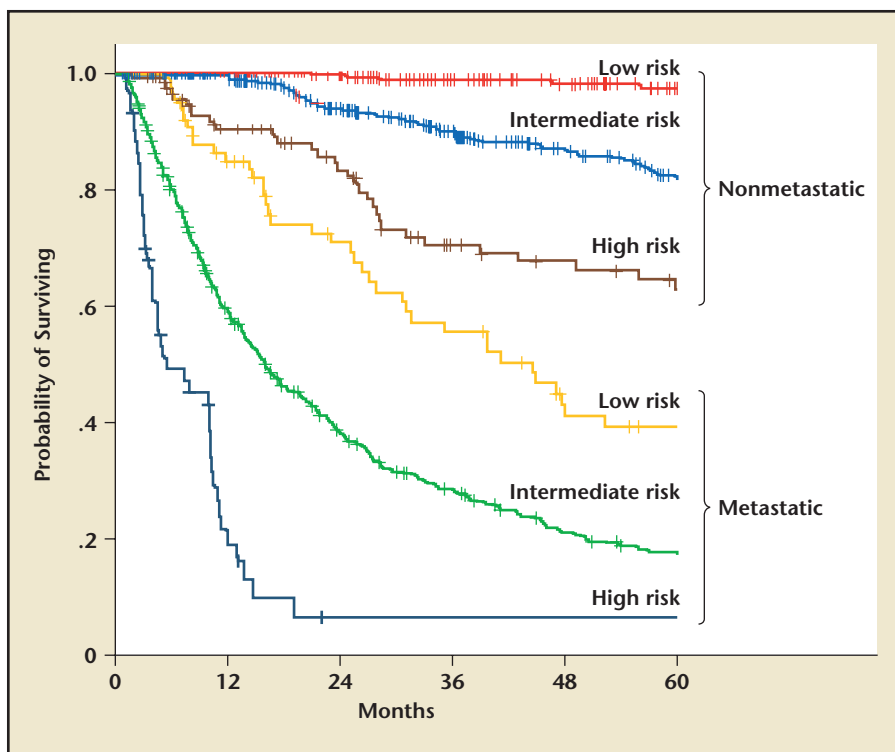
(mTOR) pathway³¹ or experimental therapies. The SSIGN (stage, size, grade, and necrosis) score is based

on the Mayo Clinic experience that included 1801 patients with surgically treated clear cell RCC.³² The score consists of TNM stage, tumor size, Fuhrman grade, and presence/absence of necrosis. Kattan and coworkers³³ introduced an instrument for patients with surgically resected nonmetastatic RCC that incorporates patients' symptoms, histologic subtype, tumor size, and T stage into a nomogram that predicts the risk of disease recurrence after nephrectomy. The UISS and the SSIGN score have been validated by external institutions.³⁴⁻³⁶

Molecular Markers: From Bench to Bedside

The following paragraphs discuss the most relevant pathways in RCC. A summary of these pathways and their inhibitors currently used in RCC is depicted in Figure 3.

Figure 2. Kaplan-Meier survival estimates (disease-specific survival) according to the University of California Integrated Staging System risk group.



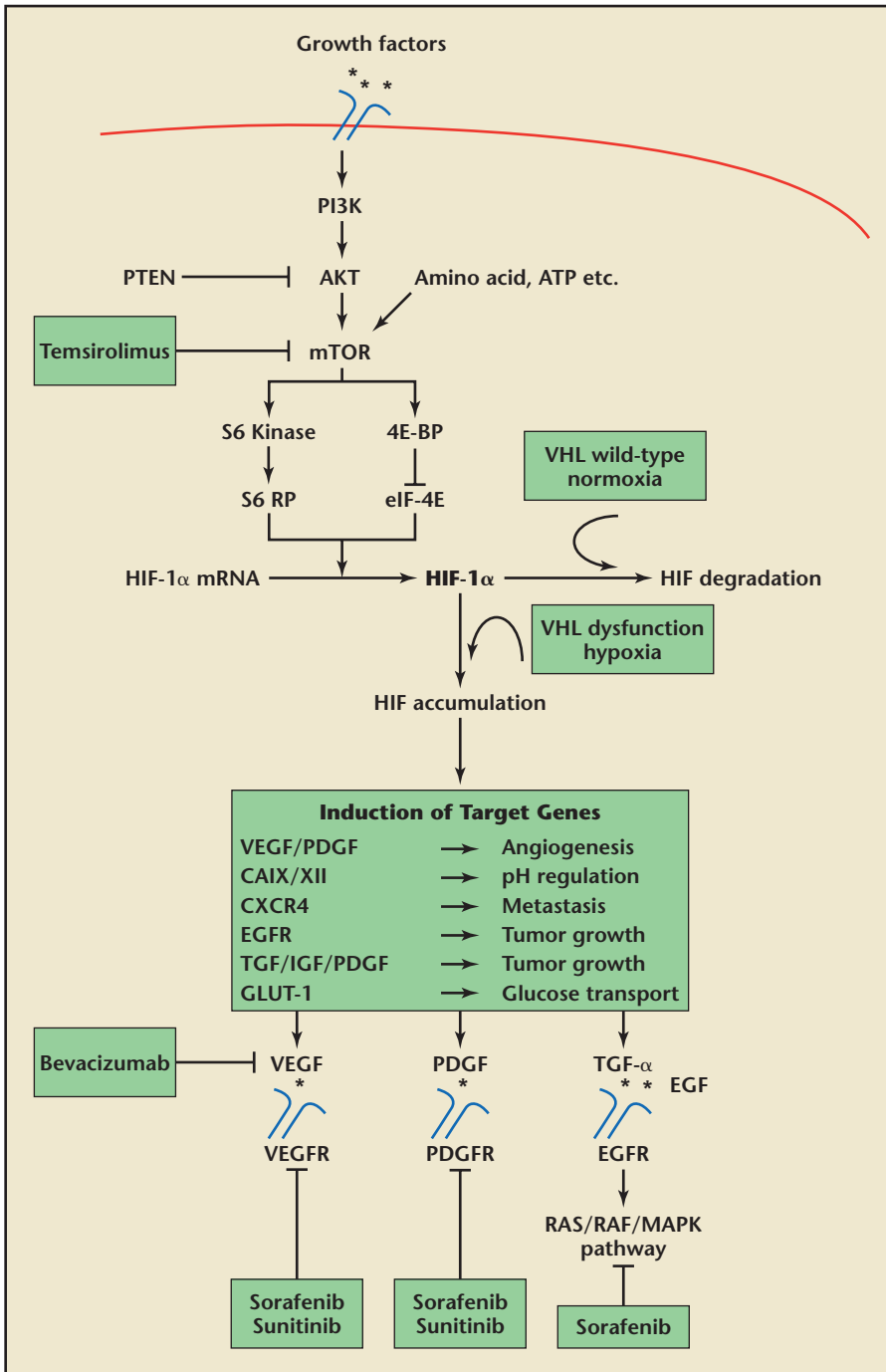


Figure 3. Regulation of hypoxia-inducible factor-1 α (HIF-1 α) and drug interventions currently in use. Activation of receptor tyrosine kinase (RTK), such as Rous Sarcoma oncogene (SRC) and the human epidermal growth factor receptor 2 (HER2), insulinlike growth factor (IGF), and epidermal growth factor (EGF) receptors, stimulate the PI3K-AKT-mTOR pathway. These pathways lead to the phosphorylation of S6 kinase and 4E-BP1. S6 kinase and 4E-BP1 lead to the translation of HIF-1 α messenger RNA (mRNA). The hypoxia-induced pathway is linked to the VHL dysfunction in renal cell carcinoma (RCC). HIF regulates the expression of an array of genes that encode proteins regulating angiogenesis, pH, metastatic spread, tumor growth, and glucose transport. The drugs currently preferred for the targeted treatment of metastatic RCC are depicted here. ATP, adenosine triphosphate; EGFR, EGF receptor; mTOR, mammalian target of rapamycin; PDGF, platelet-derived growth factor; PDGFR, PDGF receptor; PI3K, phosphoinositide 3-kinase; TGF- α , transforming growth factor- α ; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor.

Carbonic Anhydrase IX and the Hypoxia-Induced Pathway

Carbonic anhydrase IX (CAIX) is the most significant molecular marker in RCC to date.³⁷ CAIX is a transmembrane enzyme that plays a role in the adaptation of the tumor to hypoxic conditions by catalyzing the reversible reaction of carbonic acid to carbon dioxide and water, thereby regulating the temporal pH value. CAIX expression in normal tissue is limited to the gastrointestinal tract, gallbladder, and pancreatic ducts,³⁸ whereas overexpression of CAIX has been seen in many tumors, including RCC. In addition to hypoxia, CAIX expression is regulated through VHL.³⁹ Both hypoxia and loss of the function of the VHL protein lead to increased cellular levels of hypoxia-inducible factor-1 α (HIF-1 α) and subsequently to an up-regulation of the CAIX expression.^{39,40} Because clear cell RCC is genetically linked to loss of the VHL function and is commonly associated with a hypoxic tumor microenvironment, CAIX serves as a strong biomarker for clear cell RCC. In addition to up-regulation of CAIX, HIF-1 α also increases the expression of other proteins, such as the pro-angiogenic vascular endothelial growth factor (VEGF-A), platelet-derived growth factor (PDGF), transforming growth factor- α (TGF- α), epidermal growth factor receptor (EGFR), insulinlike growth factor (IGF), and glucose transporters.

CAIX serves as an important predictor for survival and response to immunotherapy among patients with metastatic RCC. Bui and colleagues⁴¹ were able to show that CAIX expression is an independent prognostic factor for patients with metastatic clear cell RCC. In their study, CAIX was expressed in 94% of the clear cell RCCs. Univariate recursive partitioning analysis defined a threshold of 85% cells expressing CAIX as the

optimum to stratify patients according to disease-specific survival. Using this cutoff, patients with an expression of 85% or less had a 3.1-fold increased risk (95% CI, 2.0-4.8) of death from RCC than patients with an expression greater than 85%. Expanding on an observation noted in this study, Atkins and associates⁴² showed that CAIX expression is also associated with response to interleukin-2 (IL-2)-based immunotherapy. Seventy-eight percent of the responders had high CAIX expression compared with 51% of the nonresponders. Furthermore, long-term survival of more than 5 years was seen only in patients with high CAIX expression. These findings have important implications for patient selection regarding therapeutic approaches for metastatic RCC. Patients with high CAIX expression (> 85%) might be optimal candidates for IL-2-based immunotherapy as a first-line therapy, which remains the only therapeutic option with a chance for a durable, complete remission.

Besides its use as a biomarker, CAIX is used as a therapeutic target in 2 different strategies. One strategy is to target CAIX using an anti-CAIX antibody. Bleumer and coworkers⁴³ recently reported on 35 patients with metastatic RCC who were treated with the CAIX antibody WX-G250 combined with low-dose IL-2. They showed a clinical benefit in 8 patients (23%), including 3 with partial response and 5 with disease stabilization. An international multicenter phase III trial testing the effect of WX-G250 in an adjuvant setting is currently enrolling patients. The second strategy is to use a vaccination stimulating the host immune system to generate CAIX targeting cytotoxic T lymphocytes (CTLs). Uemura and colleagues⁴⁴ showed safety and efficacy of a CAIX vaccine in HLA-A24-positive patients with cytokine-refractory metastatic RCC. Of 23

enrolled patients, 3 had partial response and 6 had stable disease. The median survival time was 21 months in this setting. In the Kidney Cancer Program laboratory at UCLA, a granulocyte-macrophage colony-stimulating factor (GM-CSF)-CAIX fusion gene has been created.⁴⁵⁻⁴⁷ Transduced in peripheral blood monocytes, it has been successful in generating CTLs capable of lysing CAIX-expressing cancer cells.⁴⁵ Currently, a clinical grade GM-CSF-CAIX vaccine is being manufactured with assistance from the National Cancer Institute's Rapid Access to Intervention Development Program. In conclusion, CAIX is a strong molecular marker and holds much promise as a therapeutic target for the future.

Angiogenesis

Clear cell RCC is genetically linked to factors regulating angiogenesis, such as VEGF, PDGF-B, and TGF- α , of which VEGF is the strongest pro-angiogenic protein.^{6,48,49} The importance of angiogenesis in the biology and therapy of RCC is now well established, based on several decades of worldwide research. RCC, like all

role of these proteins has been evaluated in recent studies. Leppert and associates⁵⁶ reported a tissue microarray-based study on 382 patients with RCC. Immunohistochemistry was performed with antibodies directed against VEGF-A, VEGF-C, VEGF-D, VEGFR-1, VEGFR-2, and VEGFR-3; the mean expression percentage within the tumor epithelium in clear cell and papillary RCC was 37 and 57, 71 and 75, 51 and 41, 54 and 58, 49 and 37, and 13 and 3, respectively. An additional analysis of these patients was reported by Lam and coworkers,⁵⁷ who clearly showed the predictive ability for both presence of metastasis and disease-specific survival of these proteins of the VEGF family. In their analysis, low endothelial expression of VEGFR-3 was independently associated with both lymph node metastasis and poor prognosis. The observed high expression of VEGF in clear cell RCC has been shown by other groups.^{58,59}

Hence, inhibition of angiogenesis is a promising approach for targeting metastatic RCC. This has led to the development of inhibitors of angiogenesis such as bevacizumab, sorafenib

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cancers, must induce angiogenesis to supply nutrients and oxygen required for progressive tumor growth. In-growth of new blood and lymphatic vessels also provides access to the vasculature and thereby promotes metastasis.⁵⁰⁻⁵²

VEGF has several isoforms. VEGF-A is involved in angiogenesis, whereas VEGF-C and VEGF-D are more prominent in regulating lymphangiogenesis. VEGF receptor 1 (VEGFR-1) and VEGFR-2 are the primary VEGF receptors, whereas VEGFR-3 is more involved in lymphangiogenesis.⁵³⁻⁵⁵ The

(BAY 43-9006), and sunitinib (SU11248). Antiangiogenic agents act at various steps of the angiogenesis pathway, inhibiting tumor growth and new vessel growth. Bevacizumab is a monoclonal antibody against VEGF-A. In a randomized phase II trial, patients who had received high-dose bevacizumab had a significant prolongation of progression-free survival (hazard ratio, 2.55; $P < .001$) compared with placebo. However, the drug did not improve overall survival.⁶⁰ Sorafenib is an orally bioavailable multikinase inhibitor

that targets the VEGF receptor (VEGFR), PDGFR- β , and Raf kinase. Sorafenib has been shown to be effective and tolerable in recent phase II and phase III trials.^{61,62} In a phase III trial, sorafenib produced responses in only 2% but stable disease in another 78% of the patients, which led to a significant improvement in progression-free survival compared with placebo.⁶² Sunitinib inhibits VEGFR and PDGFR- β . Sunitinib also showed significant activity, with a response

In a phase III trial, sorafenib produced responses in only 2% but stable disease in another 78% of the patients, which led to a significant improvement in progression-free survival compared with placebo.

rate of approximately 25% and prolonged survival when compared with interferon- α .⁶³⁻⁶⁵ In December 2005 and January 2006, the Food and Drug Administration approved both agents for the treatment of advanced RCC. These new potent agents are replacing IL-2-based immunotherapy as first-line treatment for many patients following nephrectomy.

mTOR Pathway

The mammalian target of rapamycin (mTOR) pathway has a central role in the regulation of cell growth, and increasing evidence suggests its dysregulation in cancer.⁶⁶ Receiving input from multiple signals, including growth factors, hormones, nutrients, and other stimulants or mitogens, the pathway stimulates protein synthesis by phosphorylating key translation regulators, such as ribosomal S6 kinase. The mTOR pathway also contributes to many other critical cellular functions, including protein degradation and angiogenesis. A UCLA tissue microarray-based study showed that the mTOR pathway is most affected in patients with clear cell RCC and poor prognostic factors, such as high nuclear grades.⁶⁷

Hence, use of inhibitors of this pathway may represent a new strategy for the targeted treatment of RCC. At present, there are at least 3 mTOR inhibitors that have been widely characterized in preclinical models and that are in clinical development as anticancer agents: temsirolimus (CCI-779), AP23573, and RAD001, which are esters of rapamycin that improve bioavailability and formulation. Rapamycin and esters first bind to FK506-binding protein 12 (FKBP12).

The FKBP12/rapamycin complex then binds mTOR, inducing a G1 growth arrest rather than apoptosis. Completed clinical trials show safety and efficacy of mTOR-targeting therapy in patients with RCC. In a randomized phase II trial of the mTOR inhibitor

Data from a study using temsirolimus in a high-risk patient population demonstrated an impressive 50% improvement in median survival from 7.3 to 10.9 months, indicating that this new drug might be the first-line treatment of choice in patients with high-risk metastatic RCC.

temsirolimus, Atkins and colleagues⁶⁸ observed objective responses in 7% and a clinical benefit rate (complete and partial response, minor responses, stable disease) in about 50% of individuals with metastatic RCC. As noted above, mTOR inhibitors induce G1 arrest rather than apoptosis. Therefore, disease stabilization might be higher and objective response rates might be lower. Data presented at the 2006 meeting of the American Society of Clinical Oncology from a study using temsirolimus in a high-risk patient population demonstrated an impressive 50% improvement in median survival from 7.3 to 10.9 months,³¹ indicating

that this new drug might be the first-line treatment of choice in patients with high-risk metastatic RCC.

Raf Kinase Pathway

Another important pathway in RCC is the Ras/Raf/MAPK pathway. Signaling starts by binding of a ligand to 1 of the 4 erbB proteins; the most prominent is erbB1, which is also called the EGFR. The EGFR consists of 3 domains: 1 ligand-binding domain, 1 transmembrane domain, and 1 cytoplasmic domain, which has tyrosine kinase activity. After binding of the ligands, EGF, or TGF- α , the EGFR becomes phosphorylated on the tyrosine residues. The EGFR then interacts with docking proteins, which subsequently allow the Ras protein to bind guanosine triphosphate and become active. The Ras protein then binds to Raf kinase and activates its kinase function. Subsequently, multiple kinases (MEK, MAPK, MNK) are involved in this pathway, which finally

leads to regulation of translation and transcription of important proteins, such as S6 kinase. Targeting this pathway might also be an attractive intervention.⁶⁹⁻⁷¹

MET Proto-Oncogene, Nuclear Factor- κ B

The majority of these new drugs are reserved for patients with clear cell RCC because studies have indicated that patients with non-clear cell RCC are less amenable to the new drugs. VEGF is expressed in lesser amounts in non-clear cell RCC,⁵⁸ and the mTOR pathway seems to be less affected in non-clear cell tumors,⁶⁷ providing

strong evidence that antiangiogenic and mTOR-targeting therapy might be less effective. As explained in a previous paragraph, however, the results of Leppert and colleagues⁵⁶ suggest that patients with papillary RCC might also be candidates for treatment with angiogenesis inhibitors.

Significant achievements in basic research regarding the *MET* proto-

oncogene have led to a new treatment strategy for patients with papillary RCC. The *MET* proto-oncogene encodes a transmembrane receptor with tyrosine kinase activity (c-Met), which interacts with hepatocyte growth factor (HGF). Mutation of the *MET* proto-oncogene was frequently observed in hereditary papillary RCC but also in a subset of the sporadic tumors.⁷²⁻⁷⁴ Additionally, trisomy of chromosome 7, the chromosome that contains the *MET* and *HGF* genes, is

the most frequently found aberration in sporadic papillary RCC. In addition to papillary RCC, HGF and the MET protein expression are frequently observed in clear cell RCC^{75,76} and were noted as strong indicators for survival among these patients.⁷⁷ Further, it has been shown that VHL inactivation induces phosphorylation of the MET protein.⁷⁸ Taken together, studies on

targeting HGF, the receptor, and the activity of tyrosine kinase offer promise for both clear cell and papillary RCC.⁷⁹ Another strategy for non-clear cell RCC might be to target nuclear factor- κ B (NF- κ B). NF- κ B interacts as a transcription factor, turning on genes that cause production of proteins that are essential for cell growth and survival. The efficient VHL protein, present in non-clear cell RCC, down-regulates NF- κ B,⁸⁰ and maximum NF- κ B down-regulation is

Combining Clinical Factors and Molecular Markers

required for maximum efficacy of the drug bortezomib.⁸¹ Following in vitro studies showing that tumors with efficient VHL, such as papillary RCC, have a higher response to bortezomib,⁸² this new treatment strategy is currently being explored in clinical trials.

The potential of tissue and gene microarray technology to affect the predictive accuracy of RCC prognosis and treatment is enormous. These arrays allow the simultaneous analysis of hundreds of tumor specimens for their expression of thousands of markers and genes. It is worth noting that, even at the present time, the results of these techniques can augment traditional clinical and pathologic factors.

At UCLA, a tissue microarray on 150 patients with metastatic clear cell RCC was constructed to develop a prognostic model combining clinical and molecular markers.⁸³ For this

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Main Points

- Staging of renal cell carcinoma (RCC) is performed worldwide according to the TNM (tumor, nodes, metastasis) classification. RCC's clinical behavior, however, results from complex interactions among many factors. This realization has led to more integrated staging systems, such as the University of California Integrated Staging System and the SSIGN (stage, size, grade, and necrosis) score.
- Carbonic anhydrase IX (CAIX) is the most significant molecular marker in RCC to date. Besides serving as an important predictor for survival and response to immunotherapy among patients with metastatic RCC, CAIX holds much promise as a therapeutic target.
- Inhibition of angiogenesis is a promising approach for targeting metastatic RCC that has led to the development of agents such as bevacizumab, sorafenib, and sunitinib.
- The mTOR (mammalian target of rapamycin) pathway has a central role in the regulation of cell growth, and increasing evidence suggests its dysregulation in cancer. Hence, the use of inhibitors of this pathway may represent a new strategy for the targeted treatment of RCC.
- Another important pathway in RCC is the Ras/Raf/MAPK pathway, which also represents an attractive target for intervention.
- Significant achievements in basic research on the *MET* proto-oncogene have led to a new treatment strategy for patients with papillary and clear cell RCC.
- Tissue and gene microarray technology may someday have an enormous impact on the predictive accuracy of RCC prognosis and treatment. These arrays allow the simultaneous analysis of hundreds of tumor specimens for their expression of thousands of markers and genes. Even now, the results of these techniques can augment traditional clinical and pathologic findings.

analysis, the tumor specimens were stained for Ki67, p53, gelsolin, CAIX, CAXII, phosphatase and tensin homologue deleted on chromosome 10 (PTEN), epithelial cell adhesion molecule, and vimentin. Clinical and marker models were carried out using Cox regression analysis. The models were corrected by bootstrapping and the corresponding c-indices were compared using Harrell's U-test statistics. In multivariate Cox regression analysis, T category, ECOG performance status, CAIX, PTEN, p53, and vimentin were independent prognostic factors of disease-specific survival. Moreover, the results showed that the marker model (c-index 0.64) was significantly better than the clinical model (c-index 0.62). Further, an additional increase in the prognostic accuracy was determined when combining both models to a clinical/marker model (c-index 0.68). The markers were then integrated in a nomogram that was calibrated to provide 2-year and 4-year survival rates and median survival. Based on these criteria, the clinician may identify the suitability of patients for varying treatments, such as patients with high CAIX expression for IL-2-based immunotherapy.

Conclusions

Better understanding of RCC biology is revolutionizing the approach to its surgical and medical management. The ability to individualize patient treatment is starting to have a significant impact on clinical strategies. In the future, gene expression technology will greatly expedite the process of making such strategies a reality. ■

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