We urge investigators, including those who receive funding from the National Institutes of Health or other nonindustry sources, to ensure that the studies they conduct are registered with complete information and to check the registration records for accuracy. Specific information about how to register a study in ClinicalTrials.gov can be found at http://prsinfo.clinicaltrials.gov and is described in a recent article.[3] Investigators should avoid participating in trials if they are not confident that an accurate and complete record of the trial will be maintained in an acceptable trials registry.

The sunitinib study is a case in which the willingness of one of the investigators to disclose key information about the protocol allowed a study to be considered for publication by one of the many medical journals that adhere to the ICMJE trials-registration policy. The message should be clear to all investigators participating in clinical trials: before you enroll a patient in a study, be sure that there is a full and appropriate registration of the trial in a public database approved by the ICMJE (www.icmje.org). It could salvage a study report that otherwise would not be published.

No potential conflict of interest relevant to this article was reported.

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Renal-Cell Carcinoma — Molecular Pathways and Therapies

James Brugarolas, M.D., Ph.D.

Renal-cell carcinoma is among the most resistant of tumors to therapy. Until 2005, only a single treatment, high-dose interleukin-2, had been approved by the Food and Drug Administration (FDA) for the treatment of this disease. The approval was based on durable complete responses in 5% of patients with metastatic disease,[1] but high-dose therapy with interleukin-2 is quite toxic, and in most patients its benefit is unclear.

In this issue of the *Journal*, Motzer et al.[2] and Escudier et al.[3] report on the results of phase 3 trials of two oral, small-molecule kinase inhibitors, sunitinib malate and sorafenib, respectively. Both drugs were found to improve progression-free survival in patients with metastatic clear-cell renal-cell carcinoma (a histologic type that accounts for about 75% of all renal-cell tumors). Neither sunitinib nor sorafenib had a significant effect on overall survival, but a final analysis of survival has not yet been reported. An important point in evaluating these trials is that both sunitinib and sorafenib caused clinically significant toxic effects. The two drugs are now approved by the FDA for use in advanced renal-cell carcinoma.

A biologic rationale exists for treating clear-cell renal-cell carcinoma with sunitinib or sorafenib. In at least 60% of these tumors, the von Hippel–Lindau tumor-suppressor gene (*VHL*) is inactivated. The VHL protein is a critical component of a cellular pathway that couples changes in oxygen availability to gene expression through the regulation of a transcription factor called the hypoxia-inducible factor (HIF).[4] HIF is a heterodimeric (HIFα/β) transcription factor that regulates a program of gene expression engaged in facilitating adaptation to tissue hypoxia. The VHL protein is involved in the degradation of the HIFα subunit, specifically when oxygen is abundant, thereby coupling oxygen needs to HIF activity. Unlike normal cells, cells deficient in VHL inappropriately accumulate HIFα under conditions of normal oxygen tension and have increased expression of HIF-regulated genes, including genes encoding angiogenic factors (Fig. 1). The up-regulation of HIF in VHL-deficient cells plays a critical role in tumorigenesis. Indeed, the ability of VHL-deficient renal carcinoma cells to form tumors in xenograft models can be reduced significantly by inactivation of HIF.[5,6]

The observation that inactivation of VHL results in increased HIF activity and thereby increased expression of vascular endothelial growth factor A (VEGF), platelet-derived growth factor β (PDGFβ), and transforming growth factor α (TGF-α) provided the rationale for targeting these

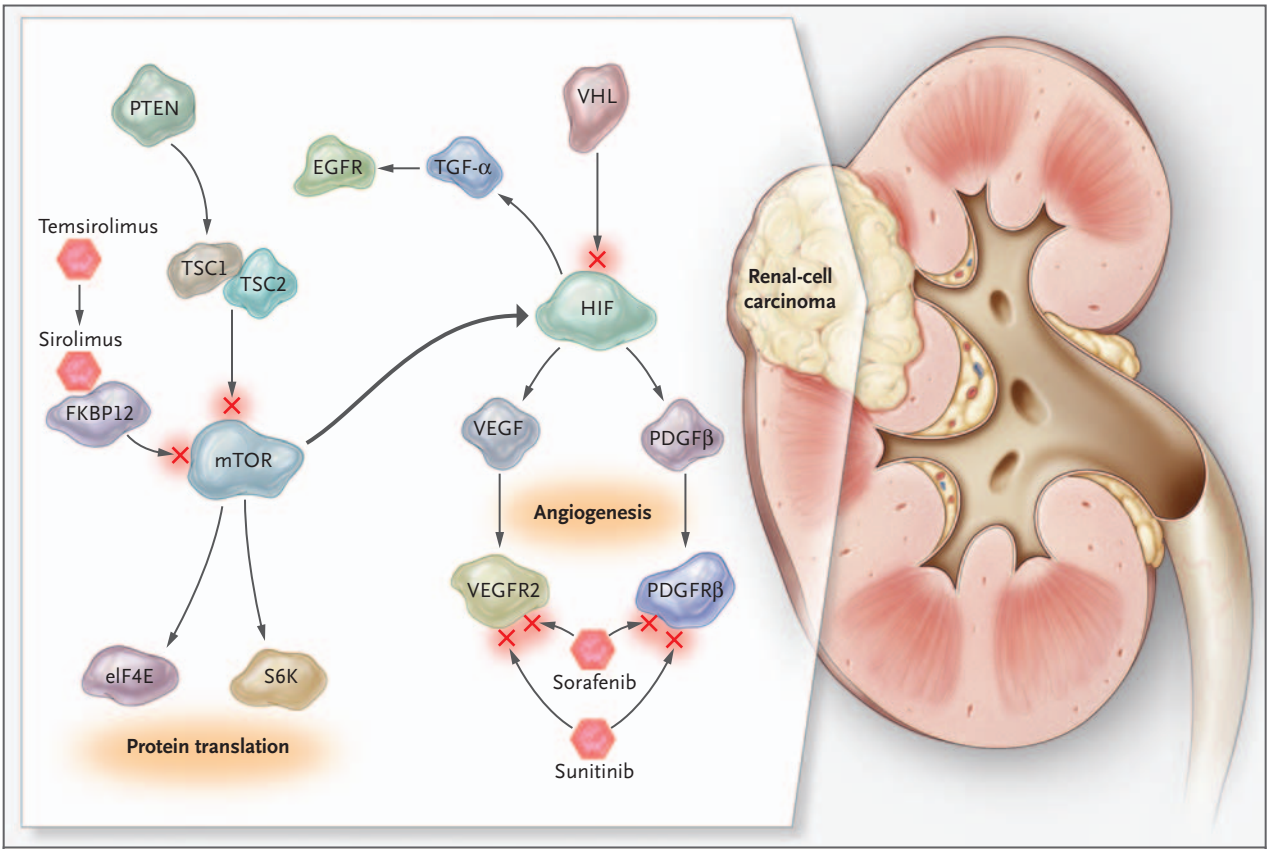

Figure 1. Molecular Pathways and Targeted Therapies in Renal-Cell Carcinoma.

VHL denotes von Hippel–Lindau protein, HIF hypoxia-inducible factor, TGF-α transforming growth factor α, VEGF vascular endothelial growth factor A, PDGFβ platelet-derived growth factor β, EGFR epidermal growth factor receptor, VEGFR2 VEGF receptor 2, PDGFRβ PDGF receptor β, PTEN phosphatase and tensin homologue, TSC1 and TSC2 tuberous sclerosis complex 1 and 2, FKBP12 FK506-binding protein 12 kD, mTOR mammalian target of rapamycin complex 1 kinase, eIF4E eukaryotic translation initiation factor 4E, and S6K S6 kinase.

pathways in clear-cell renal-cell carcinoma.[4] In principle, interruption of the production of these growth and angiogenic factors would deprive the tumor of elements that contribute to its own survival. One recent example of this reasoning can be seen in the action of bevacizumab, a humanized monoclonal antibody that targets VEGF. In a randomized, placebo-controlled, phase 2 trial of bevacizumab in patients with metastatic clear-cell renal-cell carcinoma, partial responses were observed in 10% of patients who were given a high dose of the antibody, and there was a statistically significant improvement in progression-free survival.[7] Although improvement in overall survival was not found, the data indicate that blockade of VEGF can inhibit tumor growth.

Both sunitinib and sorafenib inhibit the VEGF and PDGFβ pathways, at least in part, by acting on the VEGF receptor 2 (VEGFR2) and the PDGF receptor β (PDGFRβ), which are receptor tyrosine kinases. In vitro, sunitinib binds to the kinase domain of VEGFR2 and PDGFRβ with a greater affinity than does sorafenib,[8] which could lead to greater antitumor activity, but confirmation would require trials in which sunitinib and sorafenib are directly compared with each other.

The observation that inhibitors of the VEGF and PDGFβ signaling pathways inhibit tumor growth is a validation of the importance of HIF in clear-cell renal-cell carcinoma. A similar rationale exists for targeting TGF-α signaling pathways, because TGF-α is also overexpressed when VHL is disabled. However, clinical trials in renal-cell carcinoma with inhibitors of the receptor for TGF-α, the epidermal growth factor receptor (EGFR), have thus far not met with success.

Hudes et al. recently reported on a phase 3 trial of the kinase inhibitor temsirolimus, an analogue of sirolimus, in which this drug improved overall survival in patients with high-risk, advanced renal-

cell carcinoma.[9] Despite the improvement in overall survival, objective responses occurred in only 9% of the patients. Temsirolimus inhibits the mammalian target of rapamycin complex 1 kinase (which is referred to generically as mTOR). The best-characterized function of mTOR is in the regulation of protein translation. Through the activation of the eukaryotic translation initiation factor 4E (elF4E), which has been implicated in tumor development, and of S6 kinase (S6K), mTOR promotes the translation of messenger RNA.

Several lines of evidence have implicated mTOR in the development of renal-cell carcinoma. First, mTOR regulates HIF.[10] Second, activation of mTOR by mutations that disrupt the tuberous sclerosis complex 1 and 2 genes (*TSC1* and *TSC2*, respectively) confers a predisposition to renal-cell carcinoma and is associated with increased HIF activity.[11] In some experimental systems, inhibitors of mTOR down-regulate HIF activity primarily when the mTOR pathway is abnormally activated.[11,12] It remains to be established whether HIF mediates the tumorigenic effects of mTOR, but the foregoing observations suggest that mTOR inhibitors may be most effective (i.e., induce objective responses) against renal-cell cancers in which the mTOR pathway is abnormally activated, such as those in which the tumor suppressor phosphatase and tensin homologue (PTEN), a proximal negative regulator of mTOR, is inactivated (Fig. 1).

Although the use of temsirolimus to treat renal-cell carcinoma improves survival, no overall survival benefit has been reported with sunitinib or sorafenib. For this reason, further follow-up or additional trials are needed to establish the role of sunitinib and sorafenib in the treatment of this disease.

Clinical trials of sunitinib, sorafenib, and temsirolimus in patients with advanced renal-cell carcinoma show how promising treatments can emerge from an understanding of the molecular genetics and biology of tumors. Improvements in current treatments will arise from a greater understanding of how these three drugs affect tumors. Sunitinib and sorafenib interact with a region of kinases with shared structural features, the ATP-binding domain, and consequently inhibit multiple kinases.[8] In contrast, sirolimus (which largely mediates the effects of temsirolimus) binds to an intracellular protein, FK506-binding protein 12 kD (FKBP12), and as a sirolimus–FKBP12 complex, it specifically interacts with the mTOR complex 1. Sunitinib, sorafenib, and temsirolimus down-regulate angiogenesis, but they also affect other processes and can inhibit cell proliferation in vitro, where angiogenesis is not required. Hence, these agents probably act through more than one mechanism — they do not specifically target the VEGF and PDGFβ pathways.

It will be important to evaluate how these drugs work through the analysis of both responsive and resistant tumors. Identification of relevant drug targets would be facilitated if specific mutations were found to correlate with the emergence of drug resistance. Elucidating how these drugs inhibit tumor growth is paramount for the development of the next generation of drugs and for their rational combination.

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