The biology underlying papillary renal cell carcinoma (pRCC) is largely unknown, and no specific therapies have been developed for advanced disease. The elucidation of the MET pathway status in types I and II pRCC may help to select patients who are more likely to benefit from MET inhibitors. Clin Cancer Res; 20(13); 3361–3. ©2014 AACR.

In this issue of Clinical Cancer Research, Albiges and colleagues substantially contribute to the understanding of the biology of papillary renal cell carcinoma (pRCC) through a rigorous study of a large number of patients (1). RCC is widely recognized as a heterogeneous disease characterized by multiple histologic subtypes and distinct biological behaviors as well as variable clinical courses. Clear-cell RCC (ccRCC) is the most common subtype of kidney cancer and accounts for more than 80% of cancers that arise from the renal epithelium. pRCC is the most common subtype of non-ccRCC, accounting for 10% to 15% of all RCCs. Two main types of pRCC with divergent pathologic and clinical features have been recently recognized: type I, which is characterized by low nuclear grade and usually (but not always) an indolent clinical course, and type II, which presents with higher nuclear grade and a more aggressive clinical behavior (2).

Drugs targeting angiogenesis and specifically vascular endothelial growth factor (VEGF) have dramatically improved the clinical outcome of patients with advanced ccRCC, in which the von Hippel–Lindau/hypoxia-inducible factors (VHL/HIF) axis plays an essential role. Because non–clear-cell tumors seem to have a different biology from their clear-cell counterparts and HIF/VEGF signaling is likely to play a pro-oncogenic role only in a subset of non–clear-cell cancers (3), it is not surprising that less impressive results from VEGF-targeted agents have been described for advanced non-ccRCC, including pRCC. In addition, some series have suggested that metastatic pRCC may even carry a worse prognosis than ccRCC, justifying an urgent need for novel drugs in this particular subtype (4).

The MET protein is a transmembrane receptor tyrosine kinase. The interaction with its only known ligand, hepatocyte growth factor (HGF)/scatter factor, regulates several downstream intracellular pathways, including focal adhesion kinase (FAK), Ras/Raf/MEK/ERK, and PI3K/Akt (5). The aberrant expression of elements of the MET pathway such as MET protein has been associated with poor prognosis and aggressive features in several malignancies, including RCC (6).

Trisomy of chromosome 7, in which MET is located, has been seen to be a common occurrence in pRCC (7). In addition, mutations in MET have been identified in an inherited syndrome of type I pRCC and in a few sporadic pRCC (8), justifying MET inhibitors as a therapeutic strategy in advanced pRCC. Choueiri and colleagues conducted a clinical trial to investigate the role of a dual MET/VEGF inhibitor (foretinib) in pRCC. In this phase II study, 74 patients were stratified on the basis of MET pathway activation, defined as the presence of a germline or somatic MET mutation, MET 7q31 amplification, or gain of chromosome 7 (9). The primary endpoint of an objective response rate of at least 25% was not met. However, the objective response rate of 13.5% and a median progression-free survival duration (PFS) of 9.3 months were noteworthy, because agents targeting angiogenesis have shown modest activity with PFS rates ranging from 3% to 13% in pRCC (10). Interestingly, germline MET mutations (hereditary type I pRCC) were highly predictive of response, with 50% of patients with mutations having an objective response compared with 9% of patients without mutations (5/10 vs. 5/57, respectively; ref. 9). Notably, differences between the two pRCC subtypes were not assessed.

Albiges and colleagues (1) investigated the MET gene status in a large well-annotated cohort of 220 patients with pRCC. Each sample was independently reviewed by two specialized pathologists, both blinded to the clinical outcome. This robust dataset expands our knowledge about MET gene status for both type I and II pRCC subtypes by reporting on different mechanisms of MET activation: gene expression, copy-number alterations (CNA), mutational status, and potential coactivators of MET protein. As previously reported (6), MET expression was significantly higher in both type I and type II pRCC than in clear-cell histology. However, type I pRCC presented a higher expression of MET

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when compared with the type II subtype \((P < 0.0001)\). CNAs of \(MET\) were identified in 46% of type II pRCC and in 81% of type I pRCC. The correlation of CNA and \(MET\) mRNA expression was significantly high \((P < 0.0001)\), which may provide a biologic basis for enhanced MET signaling. Of note, 11 somatic mutations of the \(MET\) gene, including four new mutations, were identified in 51 type I pRCC (21.5%), whereas smaller series had previously reported a mutation rate around 13% in this setting. Importantly, the impact of CNA and mutations in \(MET\) on MET pathway downstream activation should be addressed in further studies.

Consistent with this framework, additional investigations are needed to translate these findings into clinical practice. The first issue raised from this study is how clinicopathologic features and clinical outcome correlate with the molecular findings, because the authors have evaluated a heterogeneous cohort. Second, assessment of MET protein expression by immunohistochemistry, which was not performed, may be helpful to select patients for further studies and clinical trials and would certainly be an important addition to the field. Third, the authors evaluated gene expression in both types of pRCC, but \(MET\) sequencing was arbitrarily performed only in type I pRCC. Identification of specific mutations in type II pRCC would need to be performed in future work.

Although the MET pathway seems to play an important role in pRCC, the inhibition of this pathway could be insufficient to control tumor growth. As the MAPK/ERK and PI3K/PIK3/AKT pathways are known to be part of the MET cascade, questions still remain about how the cross-talk among distinct elements of these downstream pathways are involved in tumor progression. It is also very possible that a subset of pRCC depends on the VEGF axis signaling in tumor cells and/or endothelial cells. In fact, small tissue-based studies showed that overexpression of VEGF and VEGF receptors (by immunohistochemistry or qRT-PCR) in pRCC can be associated with worse prognostic features (11). The elucidation of these interactions could provide a rationale for combinatorial strategies in advanced pRCC (Fig. 1).

The deeper understanding of MET activation in pRCC may also help patient selection. A study enriching for
patients whose tumors harbor genomic alteration in MET may be the ideal population for testing the efficacy of agents targeting MET in pRCC. The Cancer Genome Atlas has allowed the molecular characterization of a large number of solid tumors, and an initiative for pRCC is ongoing (12). This important initiative will help us to validate the findings from the study by Albiges and colleagues, and provide a global unbiased approach to understanding the genetic basis of pRCC, with the hope of providing more effective treatment strategies that are tailored to the genetic profile of each patient’s cancer, thus advancing our ultimate goal toward precision medicine in RCC (13).

Disclosure of Potential Conflicts of Interest
T. Choueiri reports receiving a commercial research grant from Pfizer and is a consultant/advisory board member for Aveo, Exelexis, GlaxoSmithKline, Novartis, and Pfizer. No potential conflicts of interest were disclosed by the other authors.

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