MET as a target in Papillary Renal Cell Carcinoma

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André P. Fay and Sabina Signoretti declare no conflict of interest. Toni K. Choueiri: Consultancy: Pfizer, Novartis; Advisory board: Pfizer, Novartis, Aveo, GlaxoSmithKline, Exelixis; Research: Pfizer; No Speakers bureau;

Abstract

The biology underlying papillary renal cell carcinoma (RCC) is largely unknown and no specific therapies have been developed for advanced disease. The elucidation of the MET pathway status in both types 1 and 2 papillary RCC (pRCC) may help to select patients who are more likely to benefit from MET inhibitors.
In this issue of Clinical Cancer Research, Albiges and colleagues substantially contribute to the understanding of the biology of pRCC through a rigorous study of a large number of patients(1). Renal cell carcinoma (RCC) is widely recognized as a heterogeneous disease characterized by multiple histologic subtypes and distinct biologies 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. Papillary RCC (pRCC) is the most common subtype of non-clear cell RCC, accounting for 10-15% of all RCCs. Two main types of pRCC with divergent pathological and clinical features have been recently recognized: Type 1, which is characterized by low nuclear grade and usually (but not always) an indolent clinical course, and type 2, 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, where the von hippel lindau/hypoxia inducible factors (VHL/HIF) axis plays an essential role. Since non-clear cell tumors seems 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-clear cell RCC, 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 (SF), regulates cell growth, migration, invasion, proliferation, and angiogenesis promoting malignant transformation when
inappropriately activated. HGF/MET signaling activates several downstream intracellular pathways including focal adhesion kinase (FAK), Ras/Raf/MEK/ERK, and PI3 kinase/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, where MET is located, has been seen to be a common occurrence in pRCC(7). In addition, mutations in MET have been identified in inherited syndrome of type 1 pRCC and in 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 based on MET pathway activation defined as the presence of a germline or somatic MET mutation, MET 7q31 amplification, or gain of chromosome 7. 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 PFS of 9.3 months were noteworthy, since agents targeting angiogenesis have shown modest activity with PFS rates of 1.6-6.6 months and objective response rates ranging from 3 to 13% in pRCC(9). Interestingly, germline MET mutations (hereditary type 1 papillary RCC) were highly predictive of response with 50% of patients with mutations having an objective response compared to 9% of patients without mutations (5 of 10 vs. 5 of 57, respectively)(10). Notably, differences between the two pRCC subtypes were not assessed.

Albiges and colleagues investigate the MET gene status in a large well-annotated cohort of 220 patients with pRCC. Each sample was independently reviewed by 2 specialized pathologists, both blinded to the clinical outcome. This robust dataset expands our knowledge
about MET gene status for both type 1 and 2 pRCC subtypes, by reporting on different mechanisms of MET activation: gene expression, copy number alterations, mutational status, and potential co-activators of MET protein. As previously reported(6), MET expression was significantly higher in both type 1 and type 2 pRCC than in clear cell histology. However, type 1 pRCC presented a higher expression of MET when compared with type 2 subtype (p<0.0001). Copy number alterations (CNA) of MET were identified in 46% of type 2 pRCC and in 81% of type 1 pRCC. The correlation of CNA and MET mRNA expression was significantly high (p<0.0001), which may provide a biological basis for enhanced MET signaling. Of note, 11 somatic mutations of MET gene, including new 4 mutations, were identified in 51 type 1 pRCC (21.5%) while 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 clinico-pathological features and clinical outcome correlate with the molecular findings, since 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 1 pRCC. Identification of specific mutations in type 2 pRCC would need to be performed in future work.

While the MET pathway appears to play an important role in pRCC, the inhibition of this pathway could be insufficient to control tumor growth. As MAPK/ERK and PI3K/AKT
pathways are known to be part of the MET cascade, questions still remain regarding how the crosstalk among distinct elements of these downstream pathways are involved in tumor progression. It is also very possible that a subset of pRCCs depends on the VEGF axis signaling in tumor cells and/or endothelial cells. In fact, small tissue-based studies showed that VEGF and VEGF receptors overexpression (by immunohistochemistry or quantitative reverse transcription-polymerase chain reaction) 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 (Figure 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 (TCGA) 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 Albiges et al study, and provide a global unbiased approach to understanding the genetic basis of pRCC, with the hope to providing more effective treatment strategies that are tailored to the genetic profile of each patient’s cancer; thus advancing our ultimate goal towards precision medicine in RCC(13).

Figure 1: Binding of HGF to MET induces activation of PI3K/Akt/mTOR, Ras/Raf/Mek, STAT3 and CDC42 downstream pathways. In a subset of pRCC, VEGF signaling in tumor cells may also contribute to the activation of the PI3K/Akt/mTOR and Ras/Raf/Mek pathways. VEGF signaling in endothelial cells may drive angiogenesis.
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Figure 1:
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