Nature Reviews Urology | Published online 20 Jun 2017; doi:10.1038/nrurol.2017.100

Purestock/Punchstock/Getty

KIDNEY CANCER

Diving into the genome of papillary RCC unearths therapeutic pearls

> The high rate of MET mutations suggests that MET antagonists might prove beneficial

A recent paper published in *European Urology* has characterized the genomic profile of papillary renal cell carcinoma (pRCC), and could help to inform future personalized therapy options for patients with this rare subtype of kidney cancer.

Although pRCC accounts for only 15–20% of kidney cancer cases, this subtype has been less well characterized than its clear-cell counterpart and treatment options remain limited, as it responds poorly to VEGF-targeted and mTOR-targeted therapies. This discrepancy is likely to be linked to the differences in tumour biology between the RCC subtypes: whereas clear cell (cc)RCC is driven by mutations in *VHL*, pRCC is characterized by alterations in the *MET* proto-oncogene for type 1 pRCC, and in *CDKN2A*, *SETD2*, and *TFE3* for type 2 pRCC. Some patients with type 2 pRCC harbour mutations in *FH*, which is associated with particularly poor survival. Data regarding pRCC previously presented in The Cancer Genome Atlas (TCGA) primarily focus on M0 disease, and so an understanding of the genome of advanced and metastatic pRCC is lacking.

Thus, Pal and colleagues set out to perform comprehensive genome profiling in patients with advanced pRCC. Genomes of 169 consecutive patients with advanced pRCC were sequenced between 2012 and 2016. Targeted next-generation sequencing was performed and up to 315 cancer-related genes were assessed as well as select introns from 31 genes frequently rearranged in cancer. Base substitutions, short insertions, deletions, copy number changes (homozygous deletions and amplifications), and gene fusions and rearrangements were assessed.

In Pal and co-workers' cohort, 129 of the patients were male and 40 were female, with a median age of 60 years (range 19–88 years). Histopathological review classified 39 patients as having type 1 pRCC and 108 patients as having type 2 pRCC; 22 patients remained unclassified. Advanced disease (stage IV) was identified in 61% of patients.

Overall, alterations were most frequent in the *TERT* promoter (21%), *CDKN2A* (17%), *MET* (13%), *CDKN2B* (11%), and *FH* (11%). Apart from one *FH* missense mutation reported, *FH* mutations were loss-of-function truncation mutations. The median age for patients with *FH* mutations was significantly lower compared with the whole pRCC cohort (37 years versus 60 years). Patients with type 1 pRCC most commonly had alterations in *MET* (33%; eight activating mutations, five amplifications at >6 copies), *TERT* (30%), *CDKN2A/B* (13%), and *EGFR* (8%; one activating mutation, two amplifications). Interestingly, three of the patients with *MET*-altered type 1 disease also had a concurrent alteration in *EGFR* or *KRAS*. In type 2 disease, *CDKN2A/B* (18%), *TERT* (18%), *NF2* (13%), and *FH* (13%) were the most commonly altered genes.

This study presents genomic profiling of the largest cohort of patients with advanced pRCC yet carried out, and offers therapeutic insights that could prove useful in treating patients with this rare disease. In particular, the high rate of *MET* mutations suggests that MET antagonists might prove beneficial in treating patients with advanced pRCC. Conversely, the identification of patients who harbour concurrent *MET* and *EGFR* or *KRAS* mutations suggests that the therapeutic benefit of MET inhibitors could require particularly thorough investigation, as such patients might be more likely to be resistant to MET-targeted therapy.

Based on these genomic data, exploration of personalized therapy approaches could prove to be particularly useful in patients with this rare and poorly responsive subtype of renal cancer.

Annette Fenner

ORIGINAL ARTICLE Pal. S. K. *et al.* Characterization of clinical cases of advanced papillary renal cell carcinoma via comprehensive genomic profiling. *Eur. Urol.* http://dx.doi.org/10.1016/j.eururo.2017.05.033 (2017)
FURTHER READING Linehan, W. M. & Ricketts, C. J. Kidney cancer in 2016: RCC — advances in targeted therapeutics and genomics. *Nat. Rev. Urol.* **14**, 76–78 (2017)