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Metta image/Alamy

KIDNEY CANCER

New autochthonous ccRCC model

A report in *Nature Medicine* describes the creation of a new autochthonous mouse model of clear cell renal cell carcinoma (ccRCC) based on deletion of *Vhl*, *Trp53*, and *Rb1*. Genetic and molecular analyses of the mouse tumours and comparison with data from human ccRCC provides insights into RCC development and shows that this new model recapitulates features of the human disease, providing a new model for research of tumour progression and treatment responses.

Models of ccRCC in mice exist that are based on the deletion of *Vhl* in combination with, for example, *Kif3a*, *Bap1*, or *Pbrm1*. In this new study, the researchers analysed data of sporadic ccRCCs in The Cancer Genome Atlas for changes in genes that regulate p53 and the G1–S cell cycle checkpoint. They found that 68% of ccRCCs had copy number losses or gains of ≥1 of those genes, pointing to a role in tumour initiation and progression.

For functional characterization, the team used an inducible Cre–*loxP* system specific for renal epithelial cells, creating mouse models of homozygous *Vhl*, *Trp53*, or *Rb1* deletion, alone or in combination. 82% of mice in which all three genes were deleted developed a total of 159 tumours within 25–61 weeks after Cre–*loxP* system induction. When only *Trp53* and *Rb1* were deleted, fewer mice developed fewer tumours at later time points, indicating that *Vhl* deletion accelerates tumour development and increases tumour number. All tumours in mice with *Vhl*, *Trp53*, and *Rb1* deletion were grade 3 or grade 4 ccRCCs with acinar, solid, or pseudopapillary growth patterns. Other histological findings and molecular analysis using immunohistochemistry indicated tumour features that were similar to human ccRCC. Protein and mRNA data suggested proximal tubule segments as the origin of ccRCC tumours in these mice, which is similar to the human phenotype. In addition, mouse tumour exome sequencing revealed mutational profiles that were also comparable to human ccRCC.

Finally, the team tested the utility of their mouse model in studies of treatment responses. Experiments that recapitulated typical treatment of metastatic ccRCC in humans (first-line sunitinib, second-line everolimus) showed differing responses to therapy and development of resistance, again similar to the behaviour of human tumours. The researchers also tested a HIF-α inhibitor as a third-line therapy, finding responses in some tumours.

Clemens Thoma

> “All tumours in mice with *Vhl*, *Trp53*, and *Rb1* deletion were grade 3 or grade 4 ccRCCs…”

ORIGINAL ARTICLE Harland, S. *et al.* Combined mutation in *Vhl*, *Trp53* and *Rb1* causes clear cell renal cell carcinoma in mice. *Nat. Med.* http://dx.doi.org/10.1038/nm.4343 (2017)