KIDNEY CANCER

Mice with *Flcn* knockout in proximal tubules—an *in vivo* model for multiple RCC subtypes

A new mouse tumour model in which the expression of folliculin from *Flcn* in the renal proximal tubule is knocked out provides a novel platform to study renal tumorigenesis and to investigate therapeutic approaches in renal cell carcinoma (RCC), with particular relevance for patients with Birt–Hogg–Dubé (BHD) syndrome.

“This model features early onset of tumorigenesis ... and a long life span”

Genetically engineered animal models are useful tools for studying the pathogenesis of cancers, enabling investigation of the role of specific genes in tumour development, and are important for preclinical evaluation of new drugs. In the case of RCC, the diversity of tumour subtypes and possible underlying genetic mutations complicated the design of viable models. Disruption of RCC-related genes, such as *Vhl*, *c-Met*, *Fh* or *Tsc1/Tsc2*, in mice resulted in animals that, for example, did not develop RCC, had long latency in tumour development or a lack of knockout tissue specificity. In patients with BHD, mutations in *FLCN* can result in various subtypes of RCC; hence, creating a viable *Flcn*-knockout mouse could provide a kidney cancer model that represents a wide range of possible RCC subtypes.

“Like other groups, we previously created a whole-body *Flcn*-knockout mouse model, which resulted in homozygous embryonic lethality or long tumour latency in heterozygotes,” explains Jindong Chen from the University of Rochester, NY, USA, one of the corresponding authors of the new paper in *Kidney International*. “Subsequently generated mice with *Flcn* knockout specifically in several types of renal tubules only survived for 3 weeks.”

In their latest study, the team disrupted folliculin expression specifically in the renal proximal tubules, using a Cre–loxP system under control of the *Sglt2* gene promoter. Mice with homozygous knockout of *Flcn* developed bilateral kidney hyperplasia and cysts at 1–4 months, microtumours at >6 months and large tumours at >1 year of age. The tumours were of various histologies, including papillary, high-grade sarcomatoid, chromophobe and clear cell RCC, as well as oncocyoma, recapitulating the pathological diversity seen in patients with BHD. “This model features early onset of tumorigenesis, high and consistent penetrance and a long life span,” highlights Chen. Subtypes of tumours seemed to change with increasing age: mice aged <1 year mostly had chromophobe RCCs, whereas papillary RCCs were more prevalent in older mice, possibly reflecting progressive tumorigenesis.

Evaluation of the underlying mechanisms of tumour development revealed that mammalian target of rapamycin (mTOR) and transforming growth factor β signalling was activated in kidneys with disrupted folliculin expression. To investigate the suitability of their model for drug testing, the researchers treated *Flcn*-knockout mice with the mTOR inhibitor rapamycin for 10 months and found that treatment could inhibit tumorigenesis, but not reverse the development of cysts that had already formed.

“We plan to use this model to investigate more folliculin-related pathways by combining genome-sequencing and bioinformatics approaches and to determine novel drug targets,” says Chen. “The goal is to develop therapies that will benefit patients with BHD-related kidney cancer and other patients with folliculin-deficiency-related tumours.”

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