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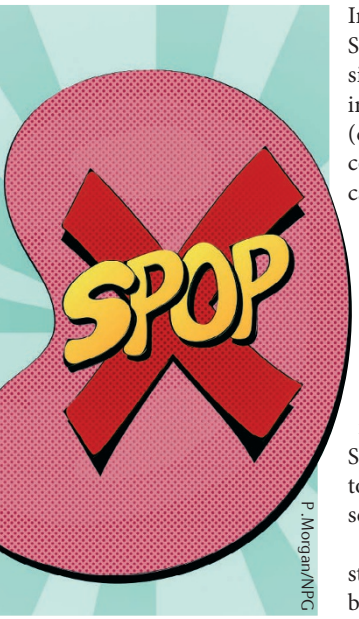
KIDNEY CANCER

On target — inhibiting SPOP in ccRCC



P. Morgan/NPG

Inhibiting the E3 ligase adaptor SPOP suppresses oncogenic signalling and induces cell death in clear cell renal cell carcinoma (ccRCC), suggesting that SPOP could be a target for novel kidney cancer therapies.

Using computational screening, Quo *et al.* identified small molecules targeting SPOP. Compound 6a was found to compete with puc_SBC1 binding to SPOP and synthetic optimization yielded lead compound 6b, which inhibited PTEN and DUSP7 binding to SPOP. Compound 6c was unable to inhibit peptide binding and served as a negative control.

NMR analysis showed no gross structural changes in SPOP on the binding of 6b and indicated that the MATH domain of SPOP is involved in this binding. Cellular thermal shift assays showed that 6b directly bound to SPOP intracellularly.

As SPOP is overexpressed and mislocated in the cytoplasm in ccRCC, it could be a novel specific therapeutic target in this disease. *In vivo*, treatment of ccRCC cell lines and primary ccRCC cells with 6a, 6b and the aqueous soluble compound 6b-HCl inhibited cell growth, but no effect on growth was seen in noncancerous HK-2 cells.

Treatment of HEK293 cells with 6a, 6b, or 6b-HCl inhibited ubiquitination of PTEN and DUSP7, causing them to accumulate. A decrease in the phosphorylation of AKT and ERK was also observed. However, 6b was unable to inhibit self-ubiquitination of RNF5 in HEK293T cells, indicating that its inhibitory effects are specific to SPOP.

In vivo, 6b had favourable pharmacodynamics and could be eliminated within 24 h. No evidence of weight loss or mortality were observed and there was no significant effect on haematopoiesis. Intraperitoneal injection of 6b or 6b-HCl reduced the growth A498-derived xenografts and also elevated the levels of PTEN and DUSP7 and reduced AKT and ERK phosphorylation in these tumours.

These data indicate that SPOP is a druggable target for ccRCC and that novel small-molecule inhibitors of SPOP could be specific therapies for treating this disease.

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ORIGINAL ARTICLE Quo, Z.-Q. *et al.* Small-molecule targeting of E3 ligase adaptor SPOP in kidney cancer. *Cancer Cell* http://dx.doi.org/10.1016/j.ccell.2016.08.003 (2016)