Nature Reviews Cancer | Published online 23 Jun 2017

IN BRIEF

TUMOUR METABOLISM

Losing that remaining fat

Recurrence of breast cancer can result from minimal residual disease. Havas *et al.* used mouse models and organoid cultures to show that residual cancer cells following tumour regression have a transcriptionally distinct state from that of normal epithelium and primary tumour cells. The transcriptomic signature of the residual cells had an altered lipid metabolism and increased levels of reactive oxygen species (ROS), features that are also observed in surviving cells in samples from patients with neoadjuvant-treated human breast cancer. The resulting increased DNA damage in the residual cells is expected to support somatic mutation-driven tumour recurrence.

ORIGINAL ARTICLE Havas, K. M. *et al.* Metabolic shifts in residual breast cancer drive tumor recurrence. *J. Clin. Invest.* **127**, 2091–2105 (2017)

CANCER MODELS

Modeling clear cell renal cell carcinoma

A new autochthonous genetically engineered mouse model of clear cell renal cell carcinoma (ccRCC) has been developed by combining deletion of the von Hippel–Lindau tumour suppressor gene (*Vhl*), *Trp53* and *Rb1* specifically in renal epithelial cells. Tumours arose from proximal tubule epithelial cells, the likely cell of origin of human ccRCC, and they recapitulated molecular markers and mRNA expression patterns of human ccRCC. Interestingly, exome sequencing demonstrated that tumours from both this mouse model and human ccRCC have recurrent mutations in genes associated with the primary cilium, an organelle that projects from the cell surface.

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

TARGETED THERAPIES

Expanding the use of PARP inhibitors

Inhibition of poly(ADP-ribose) polymerase (PARP), which is part of the single-strand break DNA repair pathway, is synthetic lethal with *BRCA1*- or *BRCA2*-induced defects in the homologous recombination (HR) DNA repair pathway. Pharmacological PARP inhibitors (PARPis) have been successfully used in cancers with BRCA mutations, but the number of patients who carry such mutations is small. Two papers have provided insights into how PARPis might be used in some non-BRCA-mutant cancers. Li *et al.* showed that the androgen receptor (AR) inhibitor enzalutamide, although not usually effective in patients with castration-resistant prostate cancer (CRPC), suppresses expression of several genes associated with HR in CRPC cell lines. This mimics BRCA deficiency, and addition of the PARPi olaparib to CRPC cells after enzalutamide treatment promoted cell death. This treatment combination also inhibited the growth of prostate cancer xenograft tumours in mice. Sun *et al.* observed that PARPi treatment resulted in upregulation of RAS–MEK–ERK signalling in cancer cells from various tissues and that PARPi-resistant cells also have RAS pathway activation. In these cells, the combination of a PARPi and a MEK inhibitor (MEKi) inhibited cell survival. Interestingly, the authors also found that cancer cells with RAS mutations are resistant to PARPis, and this can be reversed by MEKis both *in vitro* and *in vivo*.

ORIGINAL ARTICLES Li, L. *et al.* Androgen receptor inhibitor-induced "BRCAness" and PARP inhibition are synthetically lethal for castration-resistant prostate cancer. *Sci. Signal.* **10**, eaam7479 (2017) | Sun, C. *et al.* Rational combination therapy with PARP and MEK inhibitors capitalizes on therapeutic liabilities in RAS mutant cancers. *Sci. Transl Med.* **9**, eaal5148 (2017)