*Nature Reviews Clinical Oncology* **11**, 301 (2014); published online 29 April 2014; doi:10.1038/nrclinonc.2014.78; doi:10.1038/nrclinonc.2014.79; doi:10.1038/nrclinonc.2014.80

# **IN BRIEF**

# **CELL SIGNALLING**

## There's no 'l' in cancer: cells cooperate in tumorigenesis

New findings in Wht1-driven mouse mammary tumours might explain the nonhierarchical evolution of tumours that result in cancers harbouring multiple genetically distinct subclones, rather than a single 'self-interested' dominant clone. Such tumours were found to comprise distinct basal and luminal cell subclones, and functional cooperation between both cell types was required for tumour growth when implanted into secondary recipient tumour-prone mice. Specifically, the viability of *Hras*-mutant basal subclones was reliant on paracrine interactions with Wht1 produced by luminal *Hras*-wild-type subclones. Although Wht1 activation and dependency is uncommon in human breast cancer, similar cooperative mechanisms might be involved in tumorigenesis.

**Original article** Cleary, A. S. *et al.* Tumour cell heterogeneity maintained by cooperating subclones in Wnt-driven mammary cancers. *Nature* **508**, 113–117 (2014).

## BIOMARKERS

#### CAPP-Seq: an ultrasensitive quantitative assay of ctDNA

Cancer personalized profiling by deep sequencing (CAPP-Seq) is a novel economical and ultrasensitive method for quantitation of circulating tumour DNA (ctDNA) that promises to improve the routine detection and monitoring of many cancers. A form of the assay focused on somatic mutations associated with non-small-cell lung cancer (NSCLC) enabled the detection of ctDNA in 100% and 50% of patients with stage II-IV NSCLC and stage I NSCLC, respectively, with a specificity of 96%. In addition, levels of ctDNA detected using CAPP-Seq closely correlated with tumour volume before and during therapy, enabled assessment of therapeutic response earlier than was possible by imaging, and identified residual disease in cases of treatment-related imaging artefacts. The method could also be used to detect and genotype tumours without the need for biopsy, although improvements are needed to increase the sensitivity in stage I tumours.

**Original article** Newman, A. M. *et al.* An ultrasensitive method for quantitating circulating tumor DNA with broad patient coverage. *Nat. Med.* doi:10.1038/nm.3519.

#### **CELL SIGNALLING**

### Copper is required for BRAF-mediated oncogenesis

New data indicate that BRAF signalling and tumorigenesis is copper (Cu) dependent. The growth of BRAF V600Etransformed cells and BRAF-mediated tumour development in cell-transfer and spontaneous mouse models were found to be markedly decreased after genetic ablation of the Cu transporter 1 (CTR1), which mediates cellular Cu uptake and maintains intracellular Cu levels. A Cu-binding site on MEK1 was identified, disruption of which decreased ERK1/2 activation and BRAF V600E-driven tumorigenesis under normal Cu homeostasis. Importantly, the growth and tumorigenicity of BRAF V600E-mutant or BRAF-inhibitorresistant cell lines were decreased by Cu chelators. These agents are currently used routinely in the treatment of Wilson's disease, suggesting they could be repurposed as a therapy for BRAF V600E-mutant cancers.

Original article Brady, D. C. et al. Copper is required for oncogenic BRAF signalling and tumorigenesis. *Nature* doi:10.1038/nature13180.