# IN BRIEF

## GENOMIC INSTABILITY

### SPRTN links cancer and ageing

Lessel *et al.* conducted genome-wide linkage and sequencing analyses of three patients from two unrelated families with early onset hepatocellular carcinoma (HCC), genomic instability and progeroid features. All three carried rare, biallelic mutations in *SPRTN*. Although SPRTN is proposed to have a role in translesion DNA synthesis, several patient features suggested a broader role in genomic stability. The authors showed that mutant SPRTN led to replication stress and subsequent DNA damage, as well as a defect in the G2/M checkpoint, thus increasing genomic instablity.

**ORIGINAL RESEARCH PAPER** Lessel, D. *et al.* Mutations in *SPRTN* cause early onset hepatocellular carcinoma, genomic instability and progeroid features. *Nature Gen.* http://dx.doi.org/10.1038/ng.3103 (2014)

## PANCREATIC CANCER

### Stromal modulation to prevent resistance

Intrinsic resistance to chemotherapy in pancreatic ductal adenocarcinoma (PDA) has been attributed to stromal components, such as activated pancreatic stellate cells (PSCs). Sherman *et al.* found that activation of the vitamin D receptor (VDR) can convert PSCs to a quiescent state. The VDR ligand calcipotriol induced transcriptional reprogramming of PSCs and stromal remodelling. Furthermore, in a mouse model of PDA, treatment with calcipotriol plus gemcitabine increased delivery of gemcitabine to tumours and significantly improved survival compared with gemcitabine alone.

**ORIGINAL RESEARCH PAPER** Sherman, M. H. *et al.* Vitamin D receptor-mediated stromal reprogramming suppresses pancreatitis and enhances pancreatic cancer therapy. *Cell* **159**, 80–93 (2014)

## LYMPHOMA

### Release the B cell

Germinal centre B cells (GCBs) are strictly localized to lymphoid organs, unlike those of GCB-like diffuse large B cell lymphoma (GCB-DLBCL). Muppidi *et al.* found that GCB-DLBCL-associated inactivating mutations in *GNA13*, which encodes the guanine nucleotide binding protein Gα13, allow AKT activation and cell migration. Loss of Gα13 in mice caused dissemination of GCBs, and these mice developed GCB-derived lymphoma. GCB-DLBCL-associated mutations were also found in ARHGEF1, a Gα13 effector, the loss of which also caused GCB dissemination in mice, indicating that altered Gα13 signalling promotes GCB dissemination.

**ORIGINAL RESEARCH PAPER** Muppidi, J. R. *et al.* Loss of signalling via Gα13 in germinal centre B-cell-derived lymphoma. *Nature* http://dx.doi.org/10.1038/nature13765 (2014)

## TUMORIGENESIS

### Why melanoma?

RAS mutations most commonly occur at codons 12, 13 and 61, but melanoma is almost exclusively associated with NRAS codon 61 mutations. Burd *et al.* sought to understand this site specificity, and they found that mice expressing NRAS-Q61R developed melanoma, whereas mice expressing NRAS-G12D did not. There was limited difference in the ability of NRAS-Q61R and NRAS-G12D to induce downstream signalling, but NRAS-Q61R had enhanced nucleotide binding and decreased GTPase activity, indicating that it is more active than NRAS-G12D.

**ORIGINAL RESEARCH PAPER** Burd, C. E. *et al.* Mutation-specific RAS oncogenicity explains N-RAS codon 61 selection in melanoma. *Cancer Discov.* http://dx.doi.org/10.1158/2159-8290.CD-14-0729 (2014)