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)