IN BRIEF

TUMOUR SUPPRESSORS

FAT loss lets WNT get active

WNT signalling is activated in some cancers by mutation of adenomatous polyposis coli (*APC*) or β-catenin (*CTNNB1*). However, the mechanism of WNT pathway activation in cancers that do not carry these alterations is unclear. Morris *et al.* found recurrent somatic inactivating mutations in *FAT1*, which encodes a cadherin-like protein, in several cancer types. Expression of wild-type FAT1 suppressed tumorigenesis, and cancer-associated *FAT1* mutations enhanced tumour growth in mice. The authors showed that β-catenin binds FAT1, and that mutated FAT1 promotes the nuclear localization of β-catenin, leading to the expression of WNT–β-catenin target genes.

ORIGINAL RESEARCH PAPER Morris, L. G. T. *et al.* Recurrent somatic mutation of *FAT1* in multiple human cancers leads to aberrant Wnt activation. *Nature Genet.* 27 Jan 2013 (doi:10.1038/ng.2538)

EPIGENETICS

Methylation in the driver's seat?

Epigenetic alterations can be heritable and stable, but also dynamic. This plasticity has raised the question of whether epigenetic changes can be drivers of tumorigenesis. Aryee *et al.* analysed genome-wide methylation profiles in metastatic prostate cancer using 'cityscape' plots. Although they found inter-individual heterogeneity among patients, methylation alterations in the primary tumour and metastases were similar in each individual. In general, hypermethylated regions were enriched for cancer-related genes. These results suggest that DNA methylation might be a selectable driver event.

ORIGINAL RESEARCH PAPER Aryee, M. J. *et al.* DNA methylation alterations exhibit intraindividual stability and interindividual heterogeneity in prostate cancer metastases. *Sci. Transl. Med.* **5**, 169ra10 (2013)

SPLICING

Chimeric expression

Velusamy *et al.* have identified a reciprocal chimeric fusion between the transcripts of yippee-like 5 (*YPEL5*) and the phosphatase *PPP1CB* in 97 of 103 (95%) chronic lymphocytic leukaemia (CLL) samples. No evidence was found for a genomic fusion between these loci, indicating a role for RNA-splicing events in forming the chimaeras. *YPEL5–PPP1CB* produced a PPP1CB protein with reduced activity, and *PPP1CB* silencing in a CLL cell line increased proliferation and colony formation. The chimaera was not seen in normal cells or in other cancers, so it may have a specific role in CLL pathogenesis.

ORIGINAL RESEARCH PAPER Velusamy, T. *et al.* Recurrent reciprocal RNA chimera involving *YPEL5* and *PPP1CB* in chronic lymphocytic leukemia. *Proc. Natl Acad. Sci. USA* 4 Feb 2013 (doi:10.1073/pnas.1214326110)

GENETICS

Promoter mutations

Two groups have discovered recurrent mutations in the promoter of telomerase reverse transcriptase (*TERT*) in a large proportion of sporadic melanomas, as well as in a large, melanoma-prone family. The mutations create binding sites for ETS transcription factors, leading to increased transcription of *TERT*. The high frequency (more frequent than *BRAF* and *NRAS* mutations) and mutually exclusive nature of these mutations suggest that this may represent a driver mechanism in melanoma.

ORIGINAL RESEARCH PAPERS Horn, S. *et al. TERT* promoter mutations in familial and sporadic melanoma. *Science* 24 Jan 2013 (doi:10.1126/science.1230062) | Huang, F. W. *et al.* Highly recurrent *TERT* promoter mutations in human melanoma. *Science* 24 Jan 2013 (doi:10.1126/science.1229259)