target genes — tumour suppressor *Cdkn1b* (which encodes p27), the pro-apoptotic factor *Bim* and DNA repair protein *Gadd45* — were downregulated before the development of prostate tumours.

What is the mechanism by which *Pml*-loss regulates AKT? It could be either stimulation of AKT activation or prevention of pAKT inactivation. The only known AKT Thr308 phosphatase — PP2A — was shown to specifically bind PML and was enriched in PML nuclear bodies, as was pAKT. These results indicate that *Pml*-deficiency must antagonize PP2A function by preventing the recruitment of both pAKT and PP2A into PML bodies.

These data show that PML controls the nuclear tumour-suppressor network for the inactivation of nuclear pAKT, and highlights the importance of AKT localization in human cancer cells.

Ezzie Hutchinson

ORIGINAL RESEARCH PAPER Trotman, L.C. *et al.* Identification of a tumour suppressor network opposing nuclear Akt function. *Nature* 7 May 2006 (doi: 10.1038/nature04809)

be expected to have broken down by recombination since African and European populations diverged.

It is therefore likely that the microsatellite variant itself confers cancer risk, but the authors also considered two other candidate risk factors. First, they found an unknown transcript that is expressed in differently spliced forms in normal and prostate cell lines. Second, although *MYC* is too far away on the chromosome to be associated with the microsatellite, it is near enough for remote expression elements or genomic instability near the microsatellite to affect its expression. Although the actual risk factor has not been firmly identified, these results are a significant step towards doing so.

Patrick Goymer

ORIGINAL RESEARCH PAPER Amundadottir, L.T. *et al.* A common variant associated with prostate cancer in European and African populations. *Nature Genet.* 7 May 2006 (doi:10.1038/ng1808)

HEPATOCELLULAR CARCINOMA

Putting p53 in context

Hepatocellular carcinoma is one of the most prevalent cancers worldwide and is lethal in about 75% of cases. To understand the aetiology of this disease more clearly, Ron DePinho and colleagues have examined chemically induced liver damage in mouse models and found that genomic instability that is fuelled by telomere dysfunction and reduced p53 function can cooperate to induce hepatocellular carcinoma progression.

Although hepatocellular carcinomas have various aetiologies, one common factor could be cycles of hepatocyte necrosis and regeneration that might promote genetic instability and create a favourable microenvironment for carcinoma progression. Mice that have been treated with the hepatocarcinogen carbon tetrachloride (CCl_4), which mimics key aspects of human chronic liver disease, readily develop hepatocellular carcinomas. The authors observed that levels of expression of telomerase reverse transcriptase (TERT) are increased in most CCl_4 -induced hepatocellular carcinomas, and that TERT levels increased with disease progression. Given that telomere dysfunction and p53 inactivation are frequently seen in human hepatocellular carcinomas, DePinho and colleagues used *Tert*-null mice and *Trp53*-heterozygous mice to investigate further.

As expected, *Tert*-null mice had shorter telomeres with each generational intercross, with telomere dysfunction observed by the third or fourth generation. *Tert*-heterozygous mice were crossed with *Trp53*-heterozygous mice to obtain *Trp53*^{+/+} and *Trp53*^{+/-} mice that were also *Tert*^{+/-} (intact telomeres). Intercrossing of these genotypes and further successive generational

mating resulted in mice with dysfunctional telomeres.

In mice with intact telomeres, loss of one *Trp53* allele did not affect the incidence of CCl_4 -induced early neoplastic lesions or hepatocellular carcinoma. However, telomere dysfunction significantly suppressed the tumorigenesis that was observed in *Trp53*^{+/-} mice, and this suppression was reversed by loss of a single *Trp53* allele. The authors also examined the histopathological grade of the hepatocellular carcinomas and found that mice with telomere dysfunction and intact p53 had complete suppression of aggressive disease, whereas the *Trp53* heterozygotes developed aggressive hepatocellular carcinomas with no deletion or mutation of the wild-type *Trp53* allele. There was also a trend toward accelerated progression in *Trp53* heterozygotes with dysfunctional rather than intact telomeres.

DePinho and colleagues conclude that the effect of p53 loss on hepatocarcinogenesis that is induced by CCl_4 is dependent on cellular context — intact or dysfunctional telomeres — and they hypothesize that loss of p53 in hepatocellular carcinoma that is associated with chronic liver disease might function predominantly to enable hepatocyte survival in the presence of telomere dysfunction. In addition, viral transduction of *Tert* in this mouse model might permit the creation of a more accurate model of human hepatocellular carcinomas, which show telomerase reactivation.

Sarah Seton-Rogers

ORIGINAL RESEARCH PAPER Farazi, P.A. *et al.* Cooperative interactions of p53 mutation, telomere dysfunction, and chronic liver damage in hepatocellular carcinoma progression. *Cancer Res.* 66, 4766–4773 (2006)