TUMORIGENESIS

Translating cancer

When we consider factors that contribute to tumorigenesis, we typically think of defects such as oncogene activation, apoptosis inhibition and angiogenesis induction. A study published by Davide Ruggero *et al.* in the 10 January issue of *Science* reveals that deregulated ribosome function might soon be added to this list.

Ruggero *et al.* became involved in investigating ribosome regulation through their studies of dyskeratosis congenita (DC) — a rare X-linked recessive disease that is caused by point mutations in the *DKC1* gene. DC is characterized by premature ageing, mucosal leukoplakia, interstitial fibrosis of the lung and increased susceptibility to cancer. *DKC1* encodes dyskerin — a pseudouridine synthase that mediates post-transcriptional modification of ribosomal RNA, through conversion of uridine to pseudouridine. Dyskerin also physically associates with the RNA component of telomerase, TERC, to regulate telomere length. So which one of these functions, or both, could be involved in cancer susceptibility?

To answer this question, the authors generated *Dkc1*-mutant mice (*Dkc1*^{m}), which express decreased levels of the gene product. The first and second generations of *Dkc1*^{m} mice did not display any overt developmental defects at birth, but by 6 months of age they developed features of bone-marrow failure — one characteristic of human DC. Some 50% of *Dkc1*^{m} mice also developed cancer, with tumours arising from a variety of histological origins — the most common being the lung and mammary gland. These phenotypes are similar to those of people with DC, indicating that these mice are a faithful model of the human disease.

But how do defects in *Dkc1* lead to cancer? Human DC cell lines have reduced telomerase activity and shorter telomeres, so this defect was the most likely candidate to underlie the observed cancer susceptibility. But quantitative fluorescence *in situ* hybridization analysis showed that there were no detectable changes in telomere length in cells of first- or second-generation *Dkc1*^{m} mice. In fact, shortened telomeres could not be detected in these mice until the fourth generation.

So, telomere shortening was not required for cancer development in first- and second-generation *Dkc1*^{m} mice. In taking another look at the cells of these early-generation mice, the authors detected a 10–40% reduction in pseudouridine modification and processing of rRNA. These cells were also hypersensitive to drugs that inhibit protein translation, indicating disrupted ribosome function. Although the mechanism by which loss of ribosome function could promote cell transformation is not clear, the authors propose that, in *Dkc1*^{m} cells, translation of factors that regulate proliferation could be altered. Additional unrecognized functions of dyskerin could also exist, whereas reduced telomerase activity might contribute to later stages of tumour development.

Kristine Novak

References and links

ORIGINAL RESEARCH PAPER Ruggero, D. *et al*. Dyskeratosis congenita and cancer in mice deficient in ribosomal RNA modification. *Science* **299**, 259–262 (2003)

FURTHER READING Decatur, W. A. & Fournier, M. J. rRNA modifications and ribosome function. *Trends Biochem. Sci.* **27**, 344–351 (2002)

WEB SITE

Pier Paolo Pandolfi's lab:
http://www.mskcc.org/mskcc/html/10345.cfm

IN BRIEF

TECHNOLOGY

Fingerprinting the circulating repertoire of antibodies from cancer patients.

Mintz, P. J. *et al. Nature Biotechnol.* **21**, 57–63 (2003)

The identification of molecular targets for use in anticancer therapy is an important goal. One approach to achieve this has been described in *Nature Biotechnology*. The authors used a phage display system to isolate peptides that are recognized by antibodies purified from the serum of patients with prostate cancer. A consensus motif from the GRP78 protein was shown to selectively bind to antibodies from cancer patients; this was also linked to disease progression and shorter survival of patients.

ONCOGENES

Conditional activation of Neu in the mammary epithelium of transgenic mice results in reversible pulmonary metastasis.

Moody, S. E. *et al. Cancer Cell* **2**, 451–461 (2002)

Whether tumour progression can be reversed by inhibition of a single oncogene is an important question that is under debate. Moody *et al.* have investigated this with the *Neu* oncogene in transgenic mice, and show that even after mammary tumours have metastasized to the lungs, they can still be reversed by switching off the oncogene. However, following regression, most mice develop tumours that have progressed to a Neu-independent state, showing, yet again, the resilience of cancer.

THERAPEUTICS

Inhibition of skin tumor growth and angiogenesis *in vivo* by activation of cannabinoid receptors.

Casanova, M. L. *et al. J. Clin. Invest.* **111**, 43–50 (2003)

Cannabinoids have previously been shown to inhibit the growth of gliomas, so Casanova *et al.* investigated whether they could have a similar effect on non-melanoma skin cancer — one of the most common tumour types. The cannabinoid receptors CB_1 and CB_2 are expressed in the skin, and their activation by a CB_1/CB_2 agonist results in apoptosis of tumorigenic skin cells, and growth inhibition and impaired angiogenesis of malignant tumours in nude mice.

CHEMOPREVENTION

Essential role of phosphatidylinositol 3-kinase-dependent CCAAT/enhancer binding protein-β activation in the induction of glutathione *S*-transferase by oltipraz.

Kang, K. W. *et al. J. Natl Cancer Instit.* **95**, 53–66 (2003)

The chemopreventive agent oltipraz acts by inducing glutathione *S*-transferase (GST), a detoxifying enzyme, but what mediates its transcription? The authors investigated the role of C/EBP in this, and found that oltipraz induces expression of GSTA2 by causing translocation of C/EBPβ to the nucleus and its binding to response elements in the promoter, in a PI3K-dependent manner.