Moreover, β-catenin levels were increased in the nucleus of these cells, indicating that the release of β-catenin from the cell surface might result in nuclear translocation and increased transcription of β-catenin–TCF/LEF1 target genes. In fact, expression of c-*MYC* — a target of the β-catenin–TCF/LEF1 pathway — was increased in EGF-treated A431 cells and EGF increased activity of a β-catenin–specific luciferase reporter in EGFR-expressing 293T cells. So, EGF induces transcription of β-catenin target genes.

A secondary effect, caused by long-term exposure to EGF, was a marked reduction in *CAV1* and *E-cadherin* transcription in the A431 cells. Downregulation of *CAV1* by antisense RNA expression reduced E-cadherin levels in EGFR-expressing 293T cells by increasing expression of the SNAIL transcription factor, a known repressor of E-cadherin transcription. In addition, expression of antisense RNA to *CAV1* increased transcription of the β-catenin-specific reporter construct in EGFR-expressing 293T cells, whereas wildtype *CAV1* expression inhibited both basal and EGF-induced reporter activity. So, downregulation of CAV1 is required for EGF-induced β-catenin transcriptional activity. Inhibiting EGFR signalling in A431 cells reversed the effects of epithelial–mesenchymal transition and the cells formed tight cellular adhesions and expressed CAV1 and E-cadherin, confirming that the EGFR has a crucial role in downregulating these two proteins.

Finally, *in vitro* collagen-gel assays were used to determine whether CAV1 has a role in EGF-mediated tumour-cell invasion. Antisense RNA to *CAV1* significantly increased invasion of A431 cells in the absence of EGF and this effect was increased by EGF-treatment. This work provides an important insight into how CAV1 governs EGF-mediated tumour-cell invasion and forges a link between the EGF and WNT signalling pathways.

Emma Croager

References and links

ORIGINAL RESEARCH PAPER Lu, Z., Ghosh, S., Wang, Z. & Hunter. T. Downregulation of caveolin-1 function by EGF leads to the loss of E-cadherin, increased transcriptional activity of β-catenin, and enhanced tumor cell invasion. *Cancer Cell* **4**, 499–515 (2003)

WEB SITE

Tony Hunter's lab: http://pingu.salk.edu/~hunter

blocked proliferation of the *PTEN*-null cancer cells. Additional studies are required, however, before transport inhibitors can be used as cancer therapies. The drug LMB, which blocks CRM1-mediated nuclear export, has already been found to be highly toxic in Phase I clinical trials. So it will be important to learn whether this toxicity is linked to its effects on CRM1 or to its other possible activities. Nonetheless, the authors hope that some of the inhibitors that were identified in this screen might be developed as leads for new anticancer drugs.

Kristine Novak

References and links

ORIGINAL RESEARCH PAPER Kau, T. R. *et al.* A chemical genetic screen identifies inhibitors of regulated nuclear export of a Forkhead transcription factor in PTEN-deficient tumor cells. *Cancer Cell* **4**, 463–476 (2003)

FURTHER READING Kau, T. R., Way, J. C. & Silver, P. A. Nuclear transport and cancer: from mechanism to intervention. *Nature Rev. Cancer* **4**, 106–117 (2004)

WEB SITE

Pamela Silver's lab: http://research.dfci.harvard.edu/silverlab/

IN BRIEF

CHROMOSOME INSTABILITY

Dual roles of human BubR1, a mitotic checkpoint kinase, in the monitoring of chromosome instability.

Shin, H.-J. *et al. Cancer Cell* **4**, 483–497 (2003)

The mitotic checkpoint prevents chromosome instability by delaying anaphase until all chromosomes are properly attached to the mitotic spindle. Shin *et al.* show that BubR1, a component of the mitotic checkpoint machinery, is significantly reduced in cancer cells causing polyploidy. Its expression triggered apoptosis in polyploid cells and inhibited growth of polyploid tumours in mice, indicating that loss of BubR1 contributes to tumorigenesis.

METASTASIS

The role of the Wnt-signaling antagonist DKK1 in the development of osteolytic lesions in multiple myeloma.

Tian, E. *et al. N. Engl. J. Med.* **349**, 2483–2494 (2003)

Multiple myeloma (MM) cells metastasize to bone and produce osteolytic lesions, by shifting the normal balance between osteoblasts, which control bone formation, and osteoclasts, which control bone resorption. Tian *et al.* identified four genes that were overexpressed in plasma cells from patients with osteoclastic lesions, including Dikkopf1 (*DKK1*) — a secreted factor that inhibits skeletal development. DKK1 was detected in MM cells and inhibited the differentiation of osteoblastic precursors *in vitro*. So, by blocking osteoblast differentiation, DKK1-expressing MM cells promote osteoclast proliferation and osteolysis.

GENE EXPRESSION

Highly expressed genes in pancreatic ductal adenocarcinomas: a comprehensive characterization and comparison of the transcription profiles obtained from three major technologies.

Iacobuzio-Donahue, C. A. *et al. Cancer Res.* **63**, 8614–8622 (2003)

Iacobuzio-Donahue *et al.* combined data obtained from oligonucleotide gene arrays, complementary DNA arrays and serial analysis of gene expression to identify genes that are highly expressed in pancreatic cancer. This approach identified robust changes in gene expression and produced a set of six genes that might prove to be clinically useful for pancreatic cancer.

GENE THERAPY

Gene therapy insertional mutagenesis insights.

Davé, U. P., Jenkins, N. A. & Copeland, N. G. *Science* **303**, 333 (2004)

Three years after retroviral gene therapy cured nine children with X-linked severe immunodeficiency, two of the children developed T-cell leukaemia, which was caused by integration of the retrovirus near the known T-cell oncogene *LMO2*, which increases its expression. Davé and colleagues now show that the interleukin-2 receptor G gene, which is contained in the retrovirus, also has a role in the development of leukaemia, providing a genetic explanation for the high frequency of leukaemia that is observed in the gene-therapy trials.