silencing. As methylation of histone H3 is a central modification in epigenetic control, the authors immunolabelled eye discs with antibodies against histone H3 methylation. A loss or reduction of H3 lysine-4 methylation was observed in the tumour eye discs, and overexpression of Delta significantly reduced H3 methylation too.

The next step was to look at which genes were aberrantly silenced. Such genes are likely to include those involved in the control of the cell cycle, so the authors looked at the transcription of 12 tumour-related genes in the mutant and wild-type eye discs. Transcription of *Rbf*, a fly homologue of the human retinoblastoma tumour-suppressor gene (*RB*), was strongly down-regulated in the tumours. Halving *Rbf* gene dosage enhanced tumour growth, and re-establishing *Rbf* expression in the eye prevented tumour formation.

These results establish a mechanism that links the Notch–Delta pathway, epigenetic-silencing pathways and cell-cycle control in the process of tumorigenesis.

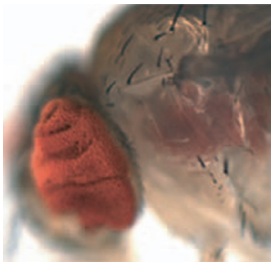
Ezzie Hutchinson

ORIGINAL RESEARCH PAPER Ferres-Marco, D. *et al.* Epigenetic silencers and Notch collaborate to promote malignant tumours by Rb silencing. *Nature* **439**, 430–436 (2006)

Control eye

Delta overexpression, showing 'large eye'

Delta, *psq* and *lola* overexpression, showing tumour growth



previous finding that expression of cyclin D1 is not required for breast development.

To investigate the function of CDK4 in breast tumorigenesis, the authors crossed *Cdk4*-null mice with mice expressing the oncogene *Erbb2* under the control of the mouse mammary tumour virus promoter. They found that loss of CDK4 inhibited breast tumour development.

As well as inactivating RB, cyclin D1–CDK4 complexes sequester p27 from cyclin E–CDK2 complexes to enable cell-cycle progression. To investigate whether this function was important for tumorigenesis, the authors collaborated with Landis and colleagues to produce cyclin-D1 knock-in mice that express a cyclin-D1 mutant protein that is still able to interact with CDK4 and so sequester p27, but the complex has no kinase activity. These mice were also resistant to *Erbb2*-driven mammary tumorigenesis, indicating that it is the kinase activity of this complex that is required to induce *Erbb2* breast tumours. Yu and colleagues also used RNA interference to show that CDK4 kinase activity is required to maintain the tumours as well as initiate them.

Does this model hold true in human breast cancer? By analysing protein expression levels in 70 sections of human breast tumours that overexpress ERBB2, the authors found that 27% showed increased expression of cyclin D1. Because most tissues develop normally in both *Cdk4*-null and *cyclin D1*-null mice, the authors suggest that CDK4 might prove to be a selective therapeutic target in all tumours that overexpress ERBB2.

Nicola McCarthy

ORIGINAL RESEARCH PAPER Yu, Q. *et al.* Requirement for CDK4 kinase function in breast cancer. *Cancer Cell* **9**, 23–32 (2006) | Landis, M. W., Pawlyk, B. S., Li, T., Sicinski, P. Hinds, P. W. Cyclin D1-dependent kinase activity in murine development and mammary tumorigenesis. *Cancer Cell* **9**, 13–22 (2006)

IN BRIEF

TARGETED THERAPY

mTOR inhibiton induces upstream receptor tyrosine kinase signaling and activates Akt.

O'Reilly, K. E. *et al. Cancer Res.* **66**, 1500–1508 (2006)

Stimulation of insulin-like growth factor 1 (IGF1) receptor induces the phosphatidylinositol 3-kinase (PI3K)–AKT–mTOR pathway, which is frequently activated in cancer cells. mTOR inhibition can arrest tumours in model systems, but shows limited anti-tumour activity in patients. O'Reilly *et al.* show that mTOR inhibition induces the expression of insulin-receptor substrate 1, which, in turn, induces IGF1 receptor activity. This upregulates AKT and negates the effect of mTOR inhibition. This feedback mechanism might explain the poor therapeutic effect of mTOR inhibitors. Furthermore, IGF1-receptor inhibition is shown to sensitize cells to mTOR inhibition, indicating promise for future combination therapies.

METASTASIS

Role of β-arrestin 1 in the metastatic progression of colorectal cancer.

Buchanan, F. G. *et al. Proc. Natl Acad. Sci. USA* **103**, 1492–1497 (2006)

The transactivation of growth-factor receptors by ligand-activated G-protein-coupled receptors (GPCRs) has been implicated in human cancer-cell survival, proliferation and migration. Now, Raymond DuBois and colleagues show that β-arrestin is involved in the SRC-dependent pathway through which this transactivation occurs. The association of a ligand-activated GPCR–β-arrestin-1–SRC signalling complex results in transactivation of the epidermal-growth-factor receptor (EGFR) and downstream AKT signalling. Furthermore, the β-arrestin-1–SRC interaction is required for both colorectal carcinoma cell migration *in vitro* and metastatic spread of the disease *in vivo*.

IMMUNOLOGY

Autoimmunity and tumour immunity induced by immune responses to mutations in self.

Engelhorn, M. E. *et al. Nature Med.* 29 Jan 2006 (doi:10.1038/nm1363)

Weakly immunogenic tumours can be converted to strongly immunogenic ones by exposure to mutagens, and mutagenized tumours can induce immunity against the original tumour in mouse models. The basis for this is unclear, but work from Alan Houghton and colleagues indicates that specific mutations can alter the intracellular trafficking routes of proteins. This means that the mutant proteins are more likely to be presented as antigens rather than recognized as self peptides.

CHROMOSOMAL TRANSLOCATIONS

H2AX prevents DNA breaks from progressing to chromosome breaks and translocations.

Franco, S. *et al. Mol. Cell* **21**, 210–214 (2006)

This paper shows that histone H2AX, a protein involved in the repair of DNA double-strand breaks, is an essential component for inhibiting chromosomal translocations that involve the immunoglobulin-heavy-chain locus (*IgH*) in activated B cells. Importantly, the authors conclude that mutation of the tumour suppressor and DNA-damage-response protein p53 does not influence the frequency of such *IgH* translocations, but instead might enable the expansion of B cells that harbour them.