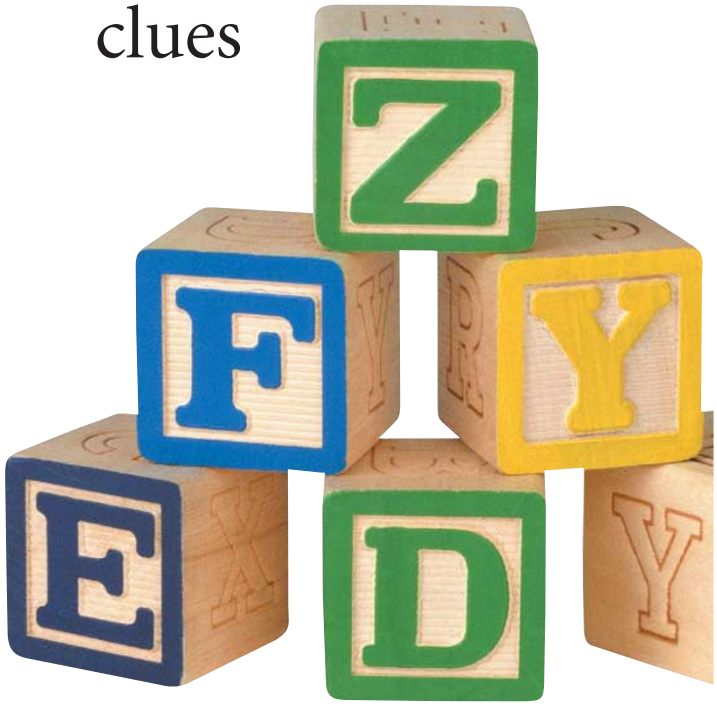
MOUSE MODELS

Reconstruction clues



One of the key challenges to breast cancer research has been to create a realistic model of this disease. Bob Weinberg and colleagues now report a new method for reconstructing human mammary epithelium in mice, which highlights the importance of the stroma in breast tumorigenesis.

The authors hypothesized that establishing human mammary stroma within the mouse mammary fat pad would provide a suitable environment for the human mammary epithelial cells (MECs) to grow. To do this, they injected a mixture of irradiated and non-irradiated mammary stromal fibroblasts into the mammary fat pads of immunocompromised mice — irradiation has been previously shown to activate expression of proteases, matrix proteins and growth factors in fibroblasts. Subsequent injection of a mixture of human breast fibroblasts and human MECs, prepared from histologically normal human reduction mammoplasty tissues, into the humanized stromal fat pads led to development of human epithelial growths with acinar, ductal and lobular structures. Weinberg and colleagues observed that this human breast tissue was fully functional during pregnancy — the cells were histologically normal, and synthesized and secreted lipids into the lumina of the human acini.

When human MEC preparations isolated from patients who had undergone mammoplasty were introduced into the humanized stromal fat pads without addition of primary human mammary fibroblasts, 30% of the samples underwent hyperplastic ductal growth. This indicates that the primary human fibroblasts suppress hyperplasia.

Two growth factors synthesized by mammary stromal cells are overexpressed by human breast cancer cells — hepatocyte growth factor causes hyperproliferation of mammary epithelium, and transforming growth factor-β1 inhibits proliferation of stromal cells and induces neoangiogenesis. The authors observed that when either of these factors was ectopically

THERAPEUTICS

Means to an end

Many chemotherapeutic drugs induce cancer-cell apoptosis, so disruption of this pathway is a primary method by which tumours become drug resistant. For example, a survival signalling pathway mediated by the kinase AKT is activated in many tumour types. Scott Lowe and colleagues show that disruption of Akt signalling with the drug rapamycin reverses tumour chemoresistance in a mouse model of lymphoma, so this drug might be used to increase the efficacy of cytotoxic cancer therapies.

Several signalling pathways regulate the fine balance between whether a cell undergoes apoptosis or survives. Much attention has recently been focused on the phosphatidylinositol 3-kinase (PI3K) pathway, which signals through the kinases AKT and TOR. TOR is inhibited by the drug rapamycin, which is used in the clinic as an immunosuppressant. Lowe and colleagues explored the consequences of using rapamycin to inhibit the Akt signalling pathway in their mouse lymphoma model.

Activation of Akt accelerates tumorigenesis and allows tumours to become refractory to chemotherapeutic agents such as cyclophosphamide and doxorubicin. But when Akt signalling was blocked with rapamycin, tumours became sensitive to the chemotherapeutic agents. Cancer cells rapidly underwent apoptosis and complete remission was achieved in mice. The authors showed that rapamycin acted specifically on the Akt signalling pathway — it had no effect on tumours that developed chemoresistance through upregulation of other anti-apoptotic proteins, such as Bcl2. Rapamycin was also not effective as a single agent.

How does AKT–TOR signalling promote cell survival? The kinase TOR normally regulates translation in response to nutrients and growth factors by phosphorylating key components of the protein-synthesis machinery, such as the ribosomal protein S6 kinase p70S6K and the 4E-BP proteins. Phosphorylated 4E-BP1 then releases the translation initiation factor eIF4E, leading to protein synthesis (see figure). So what happens when eIf4e is constitutively activated in this cancer model? Expression of eIf4e accelerated lymphomagenesis in a manner that was similar to Akt, and these tumours also became resistant to chemotherapy. They were not, however, sensitive to rapamycin — presumably because eIf4e acts downstream of Tor.

Clinical trials of rapamycin and its analogues, in combination with other chemotherapeutic agents, are underway. This study reminds us, however, that the tumour genotype should be analysed before patients are given this chemosensitizer — rapamycin would not have an effect on tumours that evade apoptosis through upregulation of BCL2, eIF4E or other pro-survival proteins.

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References and links

ORIGINAL RESEARCH PAPER Wendel, H.-G. *et al.* Survival signalling by Akt and eIF4E in oncogenesis and cancer therapy. *Nature* **428**, 332–337 (2004)

FURTHER READING McCormick, F. Survival pathways meet their end. *Nature* **428**, 267–269 (2004)

WEB SITE

Scott Lowe's lab:
http://www.cshl.org/public/SCIENCE/lowe.html