In the news

FRUIT BEARS FRUIT

Research originally aimed at improving fruit harvests has provided a potential anti-angiogenic therapy.

Oded Shoseyov and colleagues at the Hebrew University of Jerusalem were using the actin-binding protein actibind from *Aspergillus niger* to inhibit pollen tube formation in peaches and nectarines. Such activity decreases the number of fruits on a plant and therefore increases the size of the remaining fruit. However, the approach was not commercially viable as manual pruning remained cheaper.

Instead, the group changed tack — "In the course of our work, we started to get deeper into the science and understand how the actibind inhibits growth" said Shoseyov (http://www.israel21c.org, 15 July 2006). "We hypothesized that since the mechanism of growth is very similar — between the pollen cell and the cancer cell — that the protein would have the same effect" (http://www.reuters.com, 2 July 2006).

In cell culture and animal models actibind therapeutically inhibited angiogenesis, and, importantly, was not toxic to normal cells. "Both *in vitro* and *in vivo*, we've shown that actibind has an anticancer effect" said Shoseyov (http://www.israel21c.org, 15 July 2006). Interestingly, a human homologue of actibind, ribonuclease T2, is found in a region of chromosome 6 that is often deleted in cancer.

Asked whether he would be returning to his agricultural roots, Shoseyov said "It's definitely going to be cancer from now on" (http://www.israel21c.org, 15 July 2006).

Patrick Goymer

DRUG RESISTANCE

A taxing problem

> a previously uncharacterized gene, *Txr1*, which encodes a nuclear protein, was upregulated fivefold in cells with resistance to paclitaxel.

Taxanes are clinically used anticancer drugs that interact with β-tubulin, so blocking cell cycling and causing apoptosis. Upregulation of the multidrug transporter P-glycoprotein and mutations that interfere with the binding of taxanes to microtubules are known causes of resistance to taxanes. Chih-Jian Lih and others in the laboratory of Stanley N. Cohen have now discovered a gene called taxol resistance gene 1 (*Txr1*), which downregulates production of the apoptosis-inducing protein thrombospondin 1 (TSP1) and causes resistance to taxanes.

The authors used a function-based screen to search for genes whose alteration yielded resistance to the taxane paclitaxel (Taxol) in a taxane-sensitive prostate cancer cell line, M2182. They found that a previously uncharacterized gene, *Txr1*, which encodes a nuclear protein, was upregulated fivefold in M2182 cells with resistance to paclitaxel. When the expression of *Txr1* was reduced using small interfering RNAs, cells showed a 75–80% decrease in survival in the presence of paclitaxel.

What is the mechanism that underlies taxane resistance by TXR1? Gene-expression profiling showed that the most upregulated transcript was *Txr1*, whereas the most downregulated transcript was *Tsp1*. To investigate the relationship between TXR1, TSP1 and taxane cytotoxicity in cancer cells, the authors analysed NCI-60 cancer cell lines for which both taxane-sensitivity data and gene-expression data were available. In 13 out of 19 cell lines tested taxane cytotoxicity showed a negative correlation with *Txr1* expression and a positive correlation with *Tsp1* expression. The use of a luciferase reporter fused to the *Tsp1* promoter confirmed that *Txr1* negatively

MELANOMA

Compare and contrast

Tumour cells are characterized by many genomic aberrations, so finding those that are instrumental to tumorigenesis is difficult. Lynda Chin and colleagues have compared the amplifications in different mouse melanoma lines to narrow down the search, and have identified *Nedd9* (neural precursor cell expressed, developmentally downregulated 9) as a metastasis gene.

The authors generated two metastatic variants from a non-metastatic mouse model of melanoma. Profiling the genomic DNA of these variants showed that they both had amplifications on chromosome 13 relative to the parental control. The shared region, which was amplified in both lines, was 850 kb and contained 8 genes.

> *Nedd9* was the only gene that was consistently upregulated in the melanomas but not in the melanocytes.

To identify the key gene in the amplified region, expression patterns of these 8 genes were studied in a range of metastatic melanoma and non-transformed melanocyte cultures. *Nedd9* was the only gene that was consistently upregulated in the melanomas but not in the melanocytes. This pattern was also found in human melanoma samples.

To validate *Nedd9* as a candidate metastasis gene, RNA interference was used to knock down *Nedd9* expression in the original melanoma lines. A 90% reduction in expression resulted in up to a 75% reduction in metastatic potential. Conversely, in an HRAS-overexpressing non-metastatic background, overexpression of NEDD9 led to metastasis.

So, how does NEDD9 cause this effect on metastasis? The authors

regulates *Tsp1* at the level of transcription in the M2182-derived clone.

Addition of TSP1 to the culture medium of the M2182 cells with paclitaxel resistance reversed paclitaxel resistance in a dose-dependent manner and increased paclitaxel-induced apoptosis. In addition to its known effects on angiogenesis, TSP1 can also regulate cell adhesion and migration through the CD47 receptor, and this receptor is expressed on the M2182 cells. The addition of a CD47-agonist peptide to the cells led to a dose-dependent partial reversal of paclitaxel resistance. Furthermore, the addition of anti-CD47 antibodies increased the survival of paclitaxel-treated cells.

Further study of TXR1–TSP1-mediated signalling in *in vivo* models and patient samples of taxane-treated tumours is warranted.

Ezzie Hutchinson

ORIGINAL RESEARCH PAPER Lih, C.-J. *et al.* Txr1: a transcriptional regulator of thrombospondin-1 that modulates cellular sensitivity to taxanes. *Genes Dev.* 17 July 2006 (doi/10.1101/gad.1441306)
FURTHER READING Jordan, M. A. & Wilson, L. Microtubules as a target for anticancer drugs. *Nature Rev. Cancer* **4**, 253–265 (2004)

looked at the effect of NEDD9 overexpression on the activity of several known mediators of invasion and metastasis. Only FAK (focal adhesion kinase) showed significant and consistent activation by NEDD9. RNA interference against *FAK* was sufficient to reverse the effect of NEDD9 overexpression on metastasis, and both proteins were shown to co-localize to dynamic focal adhesion structures.

This research has uncovered an important new gene in metastatic melanoma — *Nedd9*. It has also demonstrated the power of comparative oncogenomics for finding the genomic aberrations that matter.

Patrick Goymer

ORIGINAL RESEARCH PAPER Kim, M. *et al.* Comparative oncogenomics identifies NEDD9 as a melanoma metastasis gene. *Cell* **125**, 1269–1281 (2006)
FURTHER READING Chin, L. The genetics of malignant melanoma: lessons from mouse and man. *Nature Rev. Cancer* **3**, 559–570 (2003)

GENETICS

Flipping the switch

In mice, the pulmonary adenoma susceptibility 1 (*Pas1*) locus confers susceptibility to lung tumours and comprises six genes, including *Kras2*, which is frequently mutated in chemically induced lung tumours. During the course of their attempt to show that *Kras2* is the *Pas1* gene, Allan Balmain and colleagues unexpectedly found that the expression levels of *Kras2* determine whether *Pas1* confers either susceptibility or resistance to tumorigenesis.

Mus spretus (*SPRET/Ei*) mice carry a dominant *Pas1* resistance haplotype, making them resistant to chemically induced lung tumours. Mice that carry the mutant *Kras2*^{LA2} allele develop lung tumours with complete penetrance and without the need for chemical carcinogenesis. To fix the origin of the mutant allele to a particular mouse strain, *Kras2*^{LA2} mice were crossed to *FVB/N* mice. The *FVB/N* mice have a *Pas1* susceptibility haplotype and, as expected, the *Kras2*^{LA2}*FVB/N* mice all developed lung tumours. To test whether or not *Kras2* is the *Pas1* gene, the authors backcrossed female *FVBSPRETF1* hybrids with *Kras2*^{LA2}*FVB/N* males. They genotyped the mice to test for linkage to *Pas1*, and expected to see one of two possibilities. If the *Pas1* gene was *Kras2*, they expected to see no linkage to the region because every mouse had the same parental mutant *Kras2* allele. If the *Pas1* gene was not *Kras2*, but another gene in the locus, they expected to see linkage to the region and resistance to tumours in those mice that inherited the *SPRET/Ei Pas1* resistance allele. To their surprise, neither of these possibilities occurred. They detected linkage to the region, but found that mice that carried the *SPRET/Ei Pas1* resistance allele were actually more susceptible to lung tumours than those that carried the *FVB/N Pas1* susceptibility allele.

Why does the *SPRET/Ei Pas1* allele sometimes confer resistance and sometimes susceptibility to lung tumours? The authors propose that *Kras2* is indeed *Pas1*, and that suppression of the oncogenic effect of a mutant Ras allele can be mediated by expression of the wild-type allele. Owing to a polymorphism, the *SPRET/Ei Kras2* allele is poorly transcribed compared with the *FVB/N Kras2* allele. Therefore, when mice carry both wild-type and mutant *Kras2* alleles from *FVB/N* mice, they are less susceptible to tumours because the wild-type allele is more highly expressed and therefore more able to suppress the mutant allele. This does not occur in mice with the less actively transcribed *SPRET/Ei* wild-type *Kras2* when they inherit the *FVB/N Kras2*^{LA2} mutation. Importantly, in chemical carcinogenesis, *SPRET/Ei* mice are resistant to lung tumour formation as mutation at *Kras2* on the *SPRET/Ei* allele results in low expression of the mutant protein.

What are the potential implications of this finding? Allele-specific transcriptional activity is common in the human genome. It is not clear how widespread context-dependent susceptibility will be, but the data presented by Balmain and colleagues indicate that further biological data might need to be taken into account in genetic-association studies to determine cancer susceptibility genes.

Sarah Seton-Rogers

ORIGINAL RESEARCH PAPER To, M. D. *et al.* A functional switch from lung cancer resistance to susceptiblity at the *Pas1* locus in *Kras2L*^{A2} mice. *Nature Genet.* 2 July 2006 (doi: 10.1038/ng1836)