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)