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ONCOGENES

Dr Jekyll and Mr Hyde

Most cancer researchers would agree that the distinction between an oncogene and a tumour suppressor is crystal clear: oncogenes are unleashed by dominant, gain-of-function mutations, whereas both alleles of a tumour suppressor must suffer a loss of function for tumorigenesis to occur. Could any gene combine these properties? Zhongqiu Zhang and colleagues report in the September issue of *Nature Genetics* that *Kras2* — one of the most frequently activated oncogenes — can cross-dress as a tumour suppressor.

The question was why, if *Kras2* really is a dominant oncogene, do some tumours with activating *Kras2*

mutations lose their other *Kras2* allele? The authors decided to search for the answer in chemically induced lung tumours in mice, which invariably contain oncogenic *Kras2* mutations that lock its product, the small GTP-binding protein K-Ras, into its active, GTP-bound form.

A comparison of *Kras2*^{+/-} mice with *Kras2*^{+/+} mice revealed that, remarkably, the *Kras2*^{+/-} mice developed more, larger lung tumours than *Kras2*^{+/+} mice after a single intraperitoneal injection of the carcinogen urethane. Furthermore, the tumours in *Kras2*^{+/-} mice were more invasive, less differentiated adenocarcinomas, whereas those in

Kras2^{+/+} mice were less advanced (adenomas), indicating that the second *Kras2* allele blocks tumour progression as well as initiation. Similar results were obtained with another carcinogen, methyl-nitrosourea.

All of these tumours contained activating mutations in *Kras2*, so the presence of a wild-type *Kras2* allele seemed to be blocking the ability of the mutated allele to drive tumour initiation and progression. Sure enough, in two cell lines

with activating *Kras2* mutations, transfection with wild-type *Kras2* inhibited cell growth by 80–90%. But how? The mitogen-activated protein kinase Erk is a well-known downstream target of activated Ras, but wild-type *Kras2* blocked the activation of Erk in one of these cell types, indicating that prevention of Erk activation is one means by which wild-type *Kras2* can exert its tumour-suppressor effect. However, cell growth was inhibited even when transfected wild-type *Kras2* did not inhibit Erk, so other mechanisms of Ras-mediated tumour suppression must exist.

So, wild-type *Kras2*, which is almost always GDP-bound, seems to have a restraining effect on its oncogenic alter ego, but how it does this is not clear. Does GDP-bound K-Ras have its own effectors that drive differentiation of pulmonary epithelium? The less differentiated tumours in the *Kras2*^{+/-} mice would indicate that they do. If so, we can imagine a constant battle in the tumour cell between the mild manners of Ras the tumour suppressor, and the wanton ways of Ras the oncoprotein.

Cath Brooksbank

MGM (Courtesy of the Kobal Collection).

References and links

ORIGINAL RESEARCH PAPER Zhang, Z. *et al.* Wildtype *Kras2* can inhibit lung carcinogenesis in mice. *Nature Genet.* **29**, 25–33 (2001)

FURTHER READING Pfeifer, G. P. A new verdict for an old convict. *Nature Genet.* **29**, 3–4 (2001)

WEB SITES

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Ming You's lab:
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