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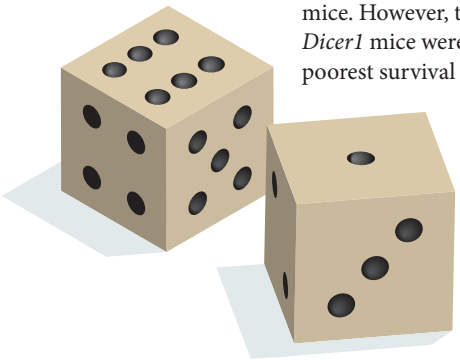
CANCER

Small losses, big gains with microRNAs

A new study in mice shows that heterozygous loss of Dicer, a crucial component of the microRNA (miRNA) processing machinery, could potentially explain the global decrease in miRNA expression often seen in tumours. Homozygous loss of *Dicer1* results in embryonic lethality, so targeted deletion of this gene has been investigated. Mice were engineered to express a floxed oncogenic *Kras* transgene (*LSL–Kras*^{G12D}) that was activated in the lung by inhalation of an adenovirus containing the Cre recombinase. Those mice with either heterozygous or presumed homozygous loss of a floxed *Dicer1* gene were found to have increased tumour burden compared with wild-type *Dicer1* mice. However, the heterozygous *Dicer1* mice were found to have the poorest survival rates. Similar results were found in a *Kras*^{G12D}-induced sarcoma model.



Analyses of the *Kras*^{G12D}-driven tumours that arose in animals that were heterozygous and homozygous for *Dicer1* indicated that the 'homozygous' tumours did not show the loss of both alleles. The tumours that arose in mice in which both *Dicer1* alleles were floxed all had incomplete recombination, and one allele was still being expressed. This indicates that complete loss of *Dicer1* expression is selected against. Indeed, enforced *Dicer1* homozygosity resulted in impaired tumour growth. These results indicate that *Dicer1* is a haploinsufficient tumour-suppressor gene.

Analyses of *DICER1* loss in human tumours using data from The Cancer Genome Project and The Cancer Genome Atlas indicated that haploinsufficiency of *DICER1* is relatively common in a variety of tumour types, and that loss of both alleles is not evident. The list of haploinsufficient tumour-suppressor genes is increasing, and the authors warn that genome-wide studies need to consider evidence for haploinsufficiency as well as the traditional loss of tumour-suppressor gene expression by mutation and loss of heterozygosity.

Nicola McCarthy,
Chief Editor, Nature Reviews Cancer

ORIGINAL RESEARCH PAPER Madhu, S. K. *et al.* *Dicer1* functions as a haploinsufficient tumour suppressor. *Genes Dev.* 10 Nov 2009 (doi 10.1101/gad.1848209)

FURTHER READING Croce, C. M. Causes and consequences of microRNA dysregulation in cancer. *Nature Rev. Genet.* **10**, 704–714 (2009) | The Cancer Genome Project: http://www.sanger.ac.uk/genetics/CGP | The Cancer Genome Atlas: http://cancergenome.nih.gov