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CANCER PREVENTION

Supermice

p53's tumour-suppressive function is famous, and many therapeutic strategies aim to activate it in tumour cells. But could it also be used as a preventive agent? A recent paper by Tyner *et al.* exposed a shortfall of such an approach — expression of a constitutively activated p53 reduced tumour incidence but induced premature ageing. Manuel Serrano and colleagues, reporting in *The EMBO Journal*, show that this strategy is still worth pursuing, as they take a different approach to increase p53 activity.

A genomic fragment that contained *Trp53* was introduced into wild-type mice, so that the effect of multiple copies controlled by their own promoter could be assessed. However, the authors first ensured that the genomic copies were functional. *Trp53*^{-/-} mouse embryonic fibroblasts (MEFs) that contained one copy of the transgene (*Trp53*^{-/-:tg}) were generated, and functional analysis revealed that they behaved like *Trp53* heterozygotes in their response to DNA damage and stress.

Following whole-body γ -irradiation, *Trp53*^{-/-:tg} mice express Waf1 — a p53 target — at similar levels to *Trp53*^{+/-} mice. The two mouse strains also have a similar percentage of radiation-induced apoptotic thymocytes — this is intermediate between *Trp53*^{+/-} and *Trp53*^{-/-} mice. However, although *Trp53*^{-/-:tg} mice have a longer lifespan than *Trp53*^{-/-} mice, they still live for less time than *Trp53*^{+/-} mice — 9.5 months compared with 14 months, which is

thought to be due to an increased loss of heterozygosity.

So how might an additional copy of functional p53 affect wild-type mice? The *Trp53*^{+/-:tg} ('super-p53') mice are healthy and fertile and, following whole-body irradiation, have an enhanced induction of Waf1 and an increased amount of apoptosis in the thymus compared with *Trp53*^{+/-} mice. These super-p53 mice also have an enhanced resistance to tumour development, as might be expected from mice with an enhanced p53-dependent response to DNA damage. Two different chemical carcinogenesis protocols were used — one produces fibrosarcomas and the other produces bladder carcinomas. With the first protocol, 11 out of 12 wild-type mice developed fibrosarcomas, but only 4

out of 12 super-p53 mice did. With the second protocol, the number of mice with multifocal tumours decreased from 57% of wild-type mice to 16% of super-p53 mice. Spontaneous tumorigenesis was also reduced in the super-p53 mice.

But does this cancer resistance come at a price? Unlike the previous report, these super-p53 mice did not display signs of premature ageing. So, increasing the activity of p53 — although a difficult proposition — might yet be a viable cancer-prevention strategy.

Emma Greenwood

References and links

ORIGINAL RESEARCH PAPER Garcia-Cao, I. *et al.* 'Super p53' mice exhibit enhanced DNA damage response, are tumor resistant and age normally. *EMBO J.* **21**, 6225–6235 (2002)

FURTHER READING Tyner, S. D. *et al.* p53 mutant mice that display early ageing-associated phenotypes. *Nature* **415**, 45–53 (2002)