TUMOUR SUPPRESSORS

Top scorer

Prostate cancer is one of the most common cancers in men, yet no gene has ever been identified that is consistently mutated in this cancer type. The tide might be about to turn, though, as Goutham Narla and colleagues now report a potential tumour-suppressor gene that is deleted in 50–60% of prostate cancers.

Chromosome 10p is deleted in over half of sporadic prostate cancers, so the authors searched this region for potential tumour-suppressor genes. The krüppel-like factor family of transcription factors has been implicated in growth, development and carcinogenesis, so they were intrigued by the fact that a member of this family, *KLF6*, resides in this region. Microsatellite analysis of tumour versus normal tissue from 22 patients with prostate cancer revealed that 17 of them had lost a copy of *KLF6*. Further mutation analysis showed that 12 of them had mutations in the remaining copy of *KLF6*, and that these mutations were not present in normal prostate tissue from the same individuals, confirming that the mutations were somatic. In total, 18 of 33 prostate tumours analysed (55%) had *KLF6* mutations.

If KLF6 is a tumour suppressor, what is its normal function and how does its inactivation lead to cancer? In an inducible expression system, upregulation of *KLF6* expression reduced cell proliferation and caused a fivefold increase in levels of the cyclin-dependent kinase inhibitor WAF1 (also known as p21), in a p53-independent manner. A luciferase reporter assay revealed that WAF1 is a direct target of KLF6, and deletion analysis pinpointed the KLF6-binding region to two GC boxes in the *WAF1* promoter. By contrast, constructs encoding four of the different mutant forms of KLF6 found in prostate cancer samples were incapable of upregulating *WAF1* expression.

But *KLF6* — now the top-scoring tumour suppressor in prostate cancer — is ubiquitously expressed; is its loss uniquely important in the aetiology of prostate cancer, or might it also be involved in the initation of other tumour types?

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References and links

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AGEING AND CANCER

Age activator

The *TP53* gene — a.k.a. 'the most frequently mutated gene in human cancer' — encodes a well-studied tumour suppressor that mediates the cellular response to stress factors such as DNA damage, hypoxia or oncogene activation. Several cancer therapeutics are being developed with the goal of restoring or increasing p53 activity. But recent findings indicate that this strategy should be reconsidered, as mice with abnormally high p53 activity are not only resistant to cancer, but also age prematurely.

Although p53 induces apoptosis in response to cellular damage, it has also been associated with replicative senescence — a terminal cell-cycle arrest state reached after a finite number of cell divisions. In the 3 January issue of *Nature*, Tyner *et al.* studied the involvement of p53 in senescence and tumour suppression using a mouse engineered to have high p53 activity. Previous attempts to transgenically overexpress p53 in mice have been unsuccessful, so Tyner *et al.* created — albeit unintentionally — mice expressing a mutant form of *Trp53* (which encodes p53 in mice) that augments wild-type p53 activity. This mutant, called the 'm'-allele, expresses a truncated RNA encoding only the C-terminal p53 fragment.

Mice carrying the m-allele (*Trp53*$^{+/m}$ mice) have enhanced p53 stability and transactivation activity. In response to ionizing radiation, levels of p53 protein increased in *Trp53*$^{+/m}$ fibroblasts beyond that of wild-type fibroblasts. This led to increased expression of p53 transcriptional targets, such as Waf1 (also known as p21), a cyclin-dependent kinase inhibitor. Several other laboratories have also shown that p53 C-terminal fragments or peptides can augment wild-type p53 activity.

But what are the phenotypes of *Trp53*$^{+/m}$ mice? As expected, they are resistant to cancer — of the 35 *Trp53*$^{+/m}$ mice examined, none developed life-threatening tumours, whereas over 80% of *Trp53*$^{+/-}$ mice and over 45% of *Trp53*$^{+/+}$ mice did. The authors showed that the enhanced tumour resistance conferred by the m-allele is dependent on the presence of the wild-type *Trp53* allele, because *Trp53*$^{-/m}$ mice develop tumours at a similar rate to *Trp53*$^{-/-}$ mice. Furthermore, *Trp53*$^{-/m}$ and *Trp53*$^{-/-}$ fibroblasts are equally susceptible to transformation.

Given the enhanced tumour resistance of *Trp53*$^{+/m}$ mice, it might be predicted that they would live longer than wild-type mice. Surprisingly, the median lifespan of the *Trp53*$^{+/m}$ mice was 23% shorter than that of their *Trp53*$^{+/+}$ littermates. Up to 12 months of age, *Trp53*$^{+/m}$ mice appear morphologically identical to controls. At 18 months, however, *Trp53*$^{+/m}$ mice undergo weight loss and develop a hunchbacked spine. The mice develop osteoporosis, hair loss, organ atrophy and reduced tolerance to stress. Histopathological examination of the *Trp53*$^{+/m}$ mice failed to reveal any specific disease-associated phenotypes.

A second line of transgenic mice containing a temperature-sensitive mutant allele of p53 also exhibits early ageing phenotypes, supporting these findings. The authors claim that some of the ageing phenotypes indicate a reduction in proliferation of stem cells, which might undergo premature replicative senescence. They propose that *Trp53*$^{+/m}$ mice might eventually reach a point in which the proliferative capacity of stem cells is so reduced that sufficient numbers of mature cells cannot be provided to maintain organ mass, function and tolerance to stress. Further studies are required to investigate the possibility that ageing might be a side effect of the natural safeguards that protect us from cancer, and to determine whether p53 contributes to premature ageing syndromes in humans.

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WEB SITE

Lawrence K. Donehower's lab: http://www.bcm.tmc.edu/cmb/applicants/facres/faculty_res_donehower.html