TUMOUR SUPPRESSORS

A greater loss

Mice heterozygous for the retinoblastoma (*Rb*) gene develop pituitary and thyroid tumours on loss of the second allele. Inactivation of *Trp53* in *Rb*-heterozygous mouse models has demonstrated some cooperative roles for loss of both tumour-suppressor genes, but not with respect to pituitary tumorigenesis. Kenneth Tsai and colleagues now report in the 24 December issue of *Proceedings of the National Academy of Sciences* that, surprisingly, loss of the tumour suppressor Arf — which activates p53 by inhibiting Mdm2 — accelerates pituitary tumorigenesis more than loss of *Trp53* in *Rb*-heterozygous mice.

Tsai *et al*. found that loss of *Arf* accelerated pituitary tumorigenesis in $Rb^{+/-}Arf^{-/-}$ mice and led to a significant decrease in their survival compared with control $Rb^{+/-}$ mice. The $Rb^{+/-}Arf^{-/-}$ mice did not develop novel lesions that were characteristic of $Rb^{+/-}Trp53^{-/-}$ mice, indicating that *Arf* loss is not equivalent to *Trp53* loss in this model. The tumour cells from $Rb^{+/-}Arf^{-/-}$ mice proliferated faster than those from the *Trp53*-null controls, but there was no difference in the rate of apoptosis.

Examination of the mice, 30 and 60 days after birth, showed that *Arf*-null mice developed atypical lesions earlier that were increased in number, larger and more aggressive. These results indicate that loss of *Arf* has different effects on an *Rb*-heterozygous phenotype than loss of *Trp53*. All early lesions had loss of heterozygosity (LOH) at *Rb*, showing that complete loss of *Rb* is still required for tumour formation in this model. The acceleration of tumorigenesis in the $Rb^{+/-}Arf^{-/-}$ mice might be explained by *Arf* loss increasing proliferation of tumour cells after LOH at the *Rb* locus.

So, is *Arf* loss an obligatory event in pituitary tumorigenesis? It seems not, as in *Rb* heterozygotes that were also heterozygous for *Arf*, LOH for *Arf* occurred in only some of the tumours examined — so, unlike loss of *Rb*, *Arf* inactivation is not an essential step. However, Tsai *et al*. suggest that LOH of *Arf* might provide a selective advantage for early tumour cells.

The authors hypothesize that Arf might regulate a p53-independent mode of tumour suppression and suggest that this might be via regulation of p53-independent functions of the oncoprotein Mdm2.

Ezzie Hutchinson

References and links

ORIGINAL RESEARCH PAPER Tsai, K. Y. *et al.* *Arf* mutation accelerates pituitary tumor development in $Rb^{+/-}$ mice. *Proc. Natl Acad. Sci. USA* **99**, 16865–16870 (2002)

FURTHER READING Classon, M. & Harlow, E. The retinoblastoma tumour suppressor in development and cancer. *Nature Rev. Cancer* **2**, 910–917 (2002)

WEB SITE

Tyler Jacks' lab: http://www.hhmi.org/research/investigators/jacks.html

TRIAL WATCH

Prostate-cancer-specific oncolytic virus

Cell Genesys, Inc. has announced data from a Phase I/II clinical trial of CG7870 oncolytic virus therapy in patients with localized recurrent prostate cancer. CG7870 is a replication-selective oncolytic adenovirus that was administered directly into the prostate. This resulted in reductions in serum levels of prostate-specific antigen (PSA) in 75% (9 out of 12) of patients with increased PSA levels at baseline. In the nine responders, PSA levels decreased by 25–50%, and all patients remained progression-free 6 months later. The treatment was well tolerated and did not result in any serious treatment-related side effects. The trial involved 20 patients who had recurrent prostate cancer following radiation therapy, but had not yet received hormone treatment. Ten patients were treated with a single administration of one of three doses of the oncolytic virus therapy.

Cell Genesys expects to initiate a follow-up Phase II trial of intra-prostatic CG7870 in combination with external beam radiation in early-stage, high-risk prostate cancer patients in early 2003. In preclinical studies, CG7870 showed a high therapeutic index of approximately 10,000:1. This means that it could have far fewer side effects than traditional chemotherapy, which kills only about six cancer cells for every normal cell that it kills. These data were presented last December at the International Conference on Gene Therapy of Cancer in San Diego, California.

WEB SITE http://www.cellgenesys.com/

Antisense for pancreatic cancer

A Phase II clinical trial of ISIS2503 in combination with gemcitabine has shown promise in the treatment of metastatic pancreatic cancer. ISIS2503 is an antisense inhibitor of *HRAS* — an oncogene that is mutated or overexpressed in many cancers. Almost 60% of patients who received ISIS2503 plus gemcitabine survived for 6 months or longer, with a median survival time of 6.7 months. This compares favourably with patients treated with gemcitabine alone, 46% of whom survived for 6 months, with a median survival time of 5.6 months. The open-label trial enrolled 48 patients with locally advanced or metastatic pancreatic cancer who had not received previous chemotherapy. Each patient received ISIS2503 by continuous intravenous infusion for 2 weeks of a 3-week cycle, in combination with typical doses of gemcitabine on days 1 and 8.

New approaches to treating pancreatic cancer are urgently needed, as it is the fourth leading cause of cancer death in men and women in the United States. In 2002, more than 30,000 people will be diagnosed with pancreatic cancer and up to 30,000 will die from the disease. For all stages combined, the 1-year survival rate is only 21%. Isis Pharmaceuticals, Inc. is currently preparing to test ISIS 2503 in Phase III trials for pancreatic cancer, and Phase II clinical trials of this drug are also underway for metastatic breast and non-small-cell lung cancer. The results of the Phase II study were reported last December at the 6th National Institutes of Health Therapeutic Oligonucleotide Interest Group Symposium in Bethesda, Maryland.

WEB SITE http://www.isispharm.com/