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p16 and familial melanoma

It remains unclear just how big the latest player in the tumour-suppressor league will turn out to be. But p16 is not about to go away.

CHROMOSOME 9p21 is often lost or otherwise disrupted in a variety of human tumours[1]. Typically, this sort of observation leads to the prediction of an incumbent tumour suppressor, and sure enough a candidate has been recently identified[2,3]. *CDKN2* (or *MTS1* for multiple tumour-suppressor) maps to 9p21 and encodes a previously identified protein, p16, which is known to bind and inhibit the normal activity of the cyclin-dependent kinase (CDK) 4. Because the CDK family of proteins promote normal cell-cycle passage, and hence cell proliferation and growth, an inhibitor of this process, such as p16, is a plausible tumour-suppressor candidate. But it has emerged that whereas *MTS1* deletions are common in tumour cell lines they are much less common in primary tumours[4], the implication being that many of the *in vitro* mutations might simply represent cell-culture artefacts.

The latest chapter in this story is to be found in three papers in the September issue of *Nature Genetics*[5–7]. In the first, Hussussian *et al.*[5] report six disease-related *MTS1* germline mutations in nine of the 18 familial melanoma families they analysed. They also show that these mutations are in 33 of the 36 melanoma cases within these families, and are only found in families linked to the 9p21 locus and not in families linked to the other familial melanoma locus at 1p36. This is strong evidence that, despite some genetic heterogeneity, *MTS1* is a familial melanoma gene. And it might have been enough to silence the sceptics but for the second study by Kamb *et al.*[6], which shows that, of eight American and five Dutch 9p-linked familial melanoma families, only two have what might be causative mutations of *MTS1*.

Nonetheless the two papers do permit some guarded conclusions to be drawn[8]. Both groups demonstrate that some 9p-associated families have mutations of *MTS1* although in others such mutations do not appear to be important. Of course mutations might have been missed (both groups restricted their screen to coding or splice sequences and not all affected family members were analysed); or perhaps a second 9p21 gene might be involved. Still, for the time being we have an apparent contradiction. *MTS1* clearly has a role in familial melanoma, but is it playing the lead or merely a walk on part? The third paper[7], a study of pancreatic adenocarcinomas, bears on this question.

Pancreatic adenocarcinomas are unusually aggressive tumours, which often show loss of the *p53* and *DCC* (deleted in colon cancer) genes[9]. Caldas *et al.*[7], now present their results of screening a total of 27 such tumours. They examined ten cell lines, but also generated xenograft transplants in nude mice for a further 27 pancreatic adenocarcinomas. They report homozygous deletions of *MTS1* in 41%, sequence changes in 38% and loss of at least one allele in 22 of the 26 (85%) informative cases. Importantly, they were able to confirm many individual observations because often more than one xenograft was derived from the same primary tumour (either at several sites within one animal or in different animals), thus ruling out artefacts of the grafting procedure. Furthermore, comparison to normal tissue equivalents was particularly useful with regard to the sequence changes in that it confirmed that they were genuine somatic mutations.

These results clearly lend general support to the importance of p16 in cancer. Interestingly, the Dutch families studied by Kamb *et al.*[6] also have a high incidence of pancreatic adenocarcinoma, a cancer for which Caldas *et al.* have demonstrated a very high frequency of *MTS1* mutations. Perhaps more attention should be turned to pancreatic adenocarcinoma pedigrees in an attempt to discover whether *MTS1* mutations are causative in pancreatic adenocarcinoma and to what extent this explains the *MTS1* mutations in the Dutch pedigrees. Who knows, this line of study might even bring down two birds with the same stone.

Also in this month's *Nature Genetics*, a team from the National Institutes of Health and Cornell Medical Center describes work with the first four patients to have received the cystic fibrosis (CF) gene into their lungs[10]. This paper provides a frank account of the likely safety of an adenoviral approach to CF gene therapy, and is all the more informative because one of the patients developed a local and systemic inflammatory syndrome. This patient received the highest dose (2×10^9 plaque-forming units) of the CFTR (cystic fibrosis transmembrane regulator) recombinant adenovirus, administered, via a catheter, to the lower lobe bronchus of one lung and a second dose to the nasal epithelia. The patient suffered from headaches, fever, fatigue, tachycardia, some hypotension and breathing difficulties associated with significant levels of serum interleukin-6. These symptoms were treated and resolved by day 14, and there were no long-term side-effects during the one-year follow-up period.

It is encouraging that no complementation, recombination or shedding of the vector was seen; nor was there a rise in neutralizing antibodies (all patients had pre-existing anti-adenoviral antibodies), although an increase in serum IgE titre was noted in two patients. With regard to expression, CFTR messenger RNA was found in nasal epithelial samples of only one of the four patients, and no expression was seen in bronchial samples from the three patients tested. CFTR protein was found in nasal and bronchial epithelia in one patient.

This study was not intended to address issues of efficacy, and indeed few conclusions can be drawn on that score. Nevertheless, it is informative. It establishes an upper limit for the adenoviral human dose range, valuable information given that animal models may not help much in drawing up guidelines for human trials. Another lesson is evident from the fact that the patient who received the lowest viral dose (2×10^6 plaque-forming units) demonstrated CFTR expression in airway epithelia. This dose was 1,000 times less than that which caused the clinical syndrome in another patient. So although adenoviral-mediated CF gene therapy still has quite some way to go, its many critics have been given pause for thought.

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Also in this month's *Nature Genetics*: mutations in the fibroblast growth factor receptor-2 gene cause Crouzon syndrome; the length of uninterrupted CGG repeats determines *FMR1* instability; two new transcripts define a large imprinted domain in Prader–Willi syndrome; and 506 STS markers on a radiation hybrid map of chromosome 11.

1. Kamb, A. *et al. Science* **264**, 436–440 (1994).
2. Serrano, M., Hannon, G. J. & Beach, D. *Nature* **366**, 704–707 (1993)
3. Nobori, T. *et al. Nature* **368**, 753–756 (1994).
4. Bonetta, L. *Nature* **370**, 180 (1994).
5. Hussussian, C.J. *et al. Nature Genet.* **8**, 15–21 (1994).
6. Kamb, A. *et al. Nature Genet.* **8**, 22–26 (1994).
7. Caldas, C. *et al. Nature Genet.* **8**, 27–32 (1994).
8. Wainwright, B. *Nature Genet.* **8**, 3–5 (1994).
9. Seymour, A.B. *et al. Cancer Res.* **54**, 2761–2764 (1994).
10. Crystal, R. G. *et al. Nature Genet.* **8**, 42–51 (1994).