MICROENVIRONMENT

A nurturing tumour?

Stromal cells, which contribute to the tumour microenvironment, are known to have a profound effect on tumour development. However, in their recent *Cell* paper, Terry Van Dyke and colleagues show that the reverse is also true — that the tumour cells can provide selective pressure for mutations in the surrounding stromal cells.

There has been some evidence that stromal fibroblasts that surround a carcinoma contain mutations that cause loss of expression of tumour suppressors such as p53. But it has been unclear if this loss is selected for during tumour evolution. To investigate further, the authors used a mouse model of prostate cancer in which a fragment of the SV40 large-T antigen was expressed in the prostate epithelium only, inactivating the tumour suppressor retinoblastoma (RB) and its related proteins p107 and p130. These mice, which have wild-type p53, were crossed into p53-heterozygous and p53-null backgrounds to investigate the effect of p53 on prostate tumour development.

> “tumour cells can provide selective pressure for mutations in the surrounding stromal cells”

Surprisingly, the authors found that loss of p53 expression had an effect on the surrounding stromal cells rather than on the epithelial tumour cells. All the animals developed prostate tumours, but the p53-null animals developed tumours with extensive stromal tissue earlier than wild-type or p53-heterozygous animals. This expansion of the stroma correlated with the induction of stromal fibroblast proliferation in the p53-null animals. These findings indicated that stromal cell proliferation was only possible once p53 expression was lost, and that loss of RB function in the epithelium promotes this proliferative environment. To verify this hypothesis, the authors took stromal and epithelial samples from the wild-type and p53-heterozygous mice and analysed expression of p53. As expected, they found that loss of RB function induced p53 activation in the epithelial cells, but a subset of stromal cells also showed p53 activation. In addition, genetic loss of *Trp53* in proliferating stromal cells was seen in established tumours from both p53-heterozygous and wild-type backgrounds, indicating that p53 loss is selected for in the stromal cells. Importantly, this occurred before the loss of p53 expression in the wild-type and heterozygous epithelial tumour tissue.

The authors conclude that these studies further illustrate the complexity of the interactions between epithelial tumour cells and the surrounding stromal cells, and add to the evidence that drugs that target the tumour microenvironment could be useful for anticancer treatment.

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ORIGINAL RESEARCH PAPER Hill, R., Song, Y., Cardiff, R. D. & Van Dyke, T. Selective evolution of stromal mesenchyme with p53 loss in response to epithelial tumorigenesis. *Cell* **123**, 1001–1011 (2005)

In the news

NEW VERSUS OLD

A new technique for cervical cancer screening, which is being widely introduced in the United States and other countries, is no more accurate than the existing technique, according to research by Elizabeth Davey and colleagues published in *The Lancet* (http://www.thelancet.com).

In a meta-analysis of previously published data they show that liquid-based cytology (LBC) does no better than traditional Pap smears in discriminating the most serious cervical lesions and does not result in fewer failed tests. This is despite claims to the contrary from the director of the UK's Cancer Screening Programmes, Julietta Patnick: "The latest statistics show that LBC has reduced the rate of inadequate results by up to 90% in the first three laboratories in England where it was introduced" (http://news.bbc.co.uk, 13 January 2006).

The study's authors also point out that only 4 of the 56 published studies were of sufficient statistical power to distinguish between the techniques. This inadequacy led Jorg Obwegeser and Volker Schneider to comment that "…enthusiasm for new technology should not replace proper study design" (http://www.reuters.com, 12 January 2006).

However, others have pointed out that LBC has other advantages over traditional smears. According to Herman Kattlove of the American Cancer Society "The reason everyone is turning to liquid-based cytology is because you can [also] do the HPV test, so a woman doesn't have to come back for another test" (http://www.klastv.com, 13 January 2006). In addition, Julietta Patnick pointed out that "Once LBC is fully implemented, women will also receive their results faster, reducing anxiety and uncertainty" (http://news.bbc.co.uk, 13 January 2006).

Stephanie Blank of New York University summed up reaction to the study, saying that it "…does not dismiss liquid-based cytology" (http://www.klastv.com, 13 January 2006).

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