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Milestone 16

Letting go of inhibition

Throughout the 1980s, deletions and mutations in TP53 (the gene that encodes p53) were reported to occur in a variety of cancers, offering the first indication that this gene encoded a tumour suppressor. Later, it was shown that expression of wild-type *TP53* in human colorectal cancer cells inhibited their growth, providing further insight into p53 function and its role in cancer progression.

Deletions of the short arm of chromosome 17, which harbours the *TP53* gene, were found to occur in over 75% of colorectal carcinomas. In a 1989 *Science* paper, Baker *et al*. reported that two colon carcinoma cell lines contained deletions of chromosome 17p, causing loss of one *TP53* allele, and that the remaining allele contained mutations in a highly conserved region. The authors proposed that normal p53 functioned to suppress neoplastic growth, and that this suppression was relieved when *TP53* was mutated or deleted. Their theory was supported by a second paper, published in *Nature* during the same year by Nigro *et al*., reporting that *TP53* deletions/mutations were found in tumours of the brain, breast, lung, colon and mesenchyme — but not in normal tissue. Together, these findings provided the first evidence that p53 functioned as a tumour suppressor.

In a 1990 *Science* paper, Baker *et al*. went on to provide the first insight into p53's role in the development of human colorectal carcinoma. The authors transfected colorectal carcinoma cell lines — which express little or no endogenous *TP53* — with vectors that encode wild-type p53 or a p53 mutant that is commonly associated with colorectal cancer. Expression of wild-type *TP53* reduced colony formation by fivefold-tenfold, compared with cells transfected with mutant *TP53* or vector alone. Although a few colonies did eventually develop from cells transfected with wild-type *TP53*, the authors found that in these colonies, *TP53* had either been deleted or rearranged. Baker *et al*. used thymidine incorporation assays to show that wild-type *TP53* expression inhibited DNA replication.

But was this effect specific to carcinoma cells? The authors also transfected their constructs into epithelial cells derived from colorectal adenoma, a benign tumour that expresses normal levels of wild-type *TP53*. Adenoma cells transfected with wild-type or mutant *TP53* produced the same number of colonies, indicating that the growth-suppressive effect of wild-type *TP53* expression is cell-type specific.

Baker *et al*. concluded that cells at the premalignant stages of tumour progression, such as the adenoma cells, are less sensitive to the inhibitory effects of wild-type p53 than malignant cells. This led to the hypothesis that genetic alterations that occur during the progression of colorectal tumours might increase the sensitivity of cells to p53 inhibition, making wild-type p53 a rate-limiting factor for further tumour progression.

Kristine Novak, Senior Editor, *Nature Reviews Cancer*

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