EPIGENETICS

It takes two

Tumour-suppressor genes act as safeguards that prevent normal cells from forming tumours. But how are they taken out of action during cancer development? Initial findings focused on genetic mutations or deletions. More recent research, however, has unveiled a role for epigenetic events in the inactivation of tumour-suppressor genes. A paper in *Nature* now sheds further light on the epigenetic mechanisms that operate in human cancer.

An important factor in the control of gene expression is DNA methylation. Several genes that normally suppress tumour development are switched off in human tumours and this is associated with methylation of their promoter regions, but relatively little is known about the mechanisms by which these genes become methylated. The enzymes that catalyse DNA methylation are DNA methyltransferases (DNMTs). The prototype of this enzyme family is Dnmt1, which accounts for most DNA methylation in mouse cells. Surprisingly, however, human cells that lack *DNMT1* maintain a significant level of overall methylation and gene silencing.

Ina Rhee and colleagues therefore set out to investigate whether other DNMTs might have a more prominent role, and inactivated *DNMT3b* in a human colorectal carcinoma cell line. As was the case for disruption of *DNMT1*, the overall levels of genomic DNA methylation dropped only by a small percentage. By contrast, the simultaneous deletion of *DNMT1* and *DNMT3b* resulted in an almost complete elimination of cellular DNA methyltransferase activity and genomic methylation. Every individual gene locus analysed showed a substantial loss of methylation and increased levels of expression, including several that have been implicated in tumour progression. Furthermore, the proliferation of cells that lack *DNMT1* and *DNMT3b* was markedly reduced. These results clearly establish that methylation is required to shut off tumour-suppressor genes in human cancer cells, and show that the activity of more than one DNA methyltransferase is required to keep tumour suppressors in check if a cell is to escape normal growth control.

Future research will undoubtedly investigate how specific methylation events are controlled in normal cells and during tumour development. Understanding these mechanisms will have important therapeutic implications: changes in DNA methylation are more readily reversible than mutations or deletions, so a deeper knowledge of how DNA methylation goes awry in cancer might pave the way to restoring the function of tumour-suppressor genes in human cancer.

Barbara Marte
Editor, Nature Cell Biology

References and links

ORIGINAL RESEARCH PAPER Rhee, I. *et al.* DNMT1 and DNTM3b cooperate to silence genes in human cancer cells. *Nature* **416**, 552–556 (2002)

FURTHER READING Ponder, B. A. Cancer genetics. *Nature* **411**, 336–341 (2001)

WEB SITE

Bert Vogelstein's lab: http://www.hhmi.org/research/investigators/vogelstein.html

TRIAL WATCH

Increased death prolongs life

Advexin, a p53-expressing adenoviral vector, increases the survival times of recurrent head and neck cancer patients, according to data from two Phase II studies. At the annual meeting of the American Association for Cancer Research in San Francisco last month, researchers from Introgen Therapeutics Inc. reported that patients receiving high-dose intratumoral injections of advexin survived an average of 2.4 months longer than patients who received low-dose injections of the drug. The researchers report an 88% improvement in median survival times among patients who were treated with high doses of the drug and a 60% reduction in tumour size. The two studies — performed at 34 centres worldwide — involved a total of 166 patients with recurrent head and neck cancer who were not eligible for surgery. There were no blood, kidney or liver toxicities observed in patients in either study, and this approach is currently being tested in Phase III studies. Phase I trials are also underway in patients with prostate, ovarian, bladder and brain cancers. Advexin has been shown to induce apoptosis in cancer cells *in vitro*, and to stop growth of both wild-type and mutant p53-expressing tumour cells *in vivo,* without damaging normal cells.

WEB SITE
http://www.corporate-ir.net/ireye/ir_site.zhtml?ticker=ingn&script=2100

Colorectal cancer prevention setback

Although non-steroidal anti-inflammatory drugs (NSAIDs) have been shown to induce regression of established adenomas in familial adenomatous polyposis (FAP) patients, they don't seem to be effective in preventing the development of adenomas in individuals with a genetic predisposition to this cancer. FAP — characterized by the development of hundreds of colorectal adenomas that eventually become tumours — is caused by a germ-line mutation in the adenomatous polyposis (*APC*) gene. Colorectal cancer will develop in nearly all carriers of this mutation by the age of 60 if prophylactic colectomy is not performed, and the average age at time of diagnosis is 35 years. In the 4 April issue of *The New England Journal of Medicine*, Giardiello *et al*. tested the ability of NSAIDs — which block prostaglandin synthesis — to prevent cancer in young people who carry this mutation but have not yet developed polyps. A randomized double-blind placebo-controlled study of 41 subjects revealed that four years of treatment with the NSAID sulindac did not slow the development of adenomas, or decrease the number or size of polyps in mutant *APC* carriers. Adenomas developed in 43% of the sulindac-treated group, and 55% of the placebo group — not a statistically significant difference. The authors propose that the lack of efficacy might have been due to the development of resistance to sulindac. So, combination treatment with several different types of NSAIDs could be a more effective chemopreventative strategy.

ORIGINAL RESEARCH PAPER Giardiello, F. M. Primary chemoprevention of familial adenomatous polyposis with sulindac. *N. Engl. J. Med*. **346**, 1054–1059 (2002)

FURTHER READING Chau, I. C. Cyclooxygenase inhibition in cancer — a blind alley or a new therpaeutic reality? *N. Engl. J. Med*. **346**, 1085–1087 (2002)