THERAPEUTIC STRATEGIES

Murderous hairpins

One significant challenge in the field of cancer therapeutics is to find a way of overcoming cellular p53 inactivity. Reporting in the 30 August issue of *Nature*, Kenneth Raj and colleagues now show that a virus — the adeno-associated virus (AAV) — might provide an answer to this problem by selectively inducing apoptosis in cells that lack active p53.

The normal function of the tumour suppressor p53 is to prevent cell multiplication and promote apoptosis. However, p53 is inactivated in most types of human cancer, which allows cancerous cells to survive.

Raj and colleagues infected cell lines — that were either null or wild type for p53 — with AAV, and used flow cytometry to assess DNA content and cell fate. The p53 wild-type cells arrested briefly at G2, then re-entered the cell cycle after several days, whereas those that lacked p53 activity underwent apoptosis. This effect could also be seen in tumours in nude mice that were induced by injection with p53^{-/-} or p53^{+/-} cells: AAV reduced the incidence of p53^{-/-} tumours by 17% compared with controls, and caused established tumours to regress.

So, how does AAV induce apoptosis? The authors could mimic the effects of AAV with etoposide, a DNA-damaging drug, indicating that AAV infection might elicit a DNA-damage

response. Moreover, treatment with caffeine — an inhibitor of the DNA-damage signalling protein ATM (ataxia-telangiectasia mutated) — allowed AAV-infected cells to continue proliferating. ATM-null cells were similarly unaffected by AAV. This indicates that AAV might act by inducing an ATM-dependent DNA-damage response.

But how is this response produced? AAV-like particles that contain recombinant baculovirus DNA did not affect cell growth, indicating that AAV DNA is responsible for triggering the DNA-damage response. AAV DNA is single-stranded, with hairpin loops at both ends, and mimics abnormal DNA. Might this information signal DNA damage to cells? Indeed, injecting cells with an oligonucleotide that corresponds to the AAV hairpin — but has no coding sequence — preferentially killed p53-null cells but not wild-type cells.

What is unclear is why this DNA-damage response kills p53-null cells, but leaves p53-wild-type cells unscathed. Further work will reveal the exact pathways involved in this process. But for now, this potential new strategy for cancer treatment is exciting news.

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References and links

ORIGINAL RESEARCH PAPER Araj, K., Ogston, P. and Beard, P. *Nature* **412**, 914–916 (2001)

FURTHER READING Vogelstein, B. and Kinzler, K. W. *Nature* **412**, 865–866 (2001)

TRIAL WATCH

Blocked drains

Oesophageal cancer is a particularly insidious disease, and its incidence is rising in the developed world. It has usually begun to metastasize by the time it is diagnosed, and cure rates are low. If the metastatic escape routes of cancer cells could be predicted, we might be able to block their migration. The many lymphatic vessels that drain a tumour are the logical pathways for cancer cells to follow, but which ones will tumour cells use to spread to distant sites? A team led by Michael Griffin at the University of Newcastle, UK, has developed a simple method that tracks the most likely metastatic highways for oesophageal cancer. By injecting a blue dye and a radiolabelled colloid into the tumour margins, they can follow lymphatic drainage during surgery and remove those lymph nodes to which the radioactivity — and hence the tumour cells — are draining. In the 40 patients monitored so far, immunohistochemistry has confirmed that the technique is 95% accurate.

WEB SITE

Press release: <http://www.ncl.ac.uk/press.office/press.release/content.phtml?ref=999787371>

Proteasome blocker for myeloma

Screening for breast cancer is currently performed using standard, film mammography, but digital mammography — a technique that uses computers and detectors to produce an image of the breast — could replace it in the future. A large, multicentre trial — the digital mammographic imaging screening trial — has been launched to compare the efficacies of these screening methods, and the aim is to recruit 49,500 women in the United States and Canada over the next 18 months.

Potential benefits of digital mammography include increased effectiveness of detecting cancer in younger women — who have denser breasts — as it has better contrast resolution. This has traditionally been a problem with film mammography.

The trial also aims to evaluate cost effectiveness. Although the cost of equipment will initially be large, digital mammography might result in fewer false-positives and, consequently, fewer callbacks. In the long run, this could save money, as well as patient anguish.

The trial will run for several years, but the results, when announced, could change the future of breast-cancer screening.

WEB SITE

The DMIST trial: <http://cancernet.nci.nih.gov/cgi-bin/srchogi.exe>

Courtesy of the American College of Radiology.