THERAPEUTIC TARGETS

Survivin' cell death

Survivin has been a controversial figure in cancer research over the past few years. It has been implicated in the control of cell division and cell death, but where does its function really lie? Survivin is also specifically upregulated in cancer cells, so could it be a useful drug target? Two papers from Dario Altieri's group, in the October issue of *The Journal of Clinical Investigation*, address some of these questions *in vivo*. They show that survivin can suppress apoptosis and that a survivin mutant might prove effective in cancer gene therapy.

In the first paper, Grossman *et al.* generated a transgenic mouse that selectively expressed survivin in the skin. Interestingly, survivin had no effect on the normal skin differentiation programme. It also did not enhance cell proliferation induced by UVB irradiation, indicating that survivin does not affect cell division. So, does survivin affect apoptosis? Exposure of the transgenic and wild-type mice to UVB irradiation, and the quantitation of apoptotic or 'sunburn' keratinocytes, revealed that there was a 60% reduction in apoptosis when survivin was expressed. Survivin can also cooperate with loss of a *Trp53* allele (the mouse gene for p53) to further reduce apoptosis. In fact, survivin selectively inhibits the intrinsic, caspase-9-dependent apoptotic pathway, as keratinocytes isolated from the mice that express survivin are still susceptible to Fas-mediated apoptosis, which acts through the extrinsic, caspase-8-dependent apoptotic pathway.

With the role of survivin in suppressing apoptosis confirmed, the possibility of manipulating survivin in cancer cells — to increase apoptosis — now becomes a reality. In the second paper they achieve just that. Mesri *et al.* constructed a replication-deficient adenovirus that encoded a survivin mutant (pAd-T34A): the threonine residue of a cdc2 phosphorylation site is mutated to alanine, and the resulting mutant is thought to act as a dominant-negative by binding to cdc2 to prevent phosphorylation of endogenous survivin.

Infection of several cancer cell lines with pAd-T34A resulted in at least a 2–3-fold increase in apoptosis — breast carcinoma MCF-7 cells suffer a 7-fold increase — as visualized by DAPI staining of the nucleus and quantitiated by flow cytometry. pAd-T34A induces cytochrome *c* release, processing of caspase-9 and cleavage of caspase-3 — which corresponds with an increase in its activity — supporting the notion that survivin regulates the intrinsic apoptotic pathway.

When combined with chemotherapeutics, pAd-T34A enhanced the level of apoptosis induced by taxol, but adriamycin and pAd-T34A did not induce more apoptosis than pAd-T34A alone.

So, could pAd-T34A work *in vivo* to inhibit tumour cell growth? Immunodeficient mice were injected with MCF-7 cells that had previously been infected with either pAd-T34A or the vector alone. Only those that expressed pAd-T34A suppressed tumour growth — mitotic index was inhibited by 90% in these mice. A single injection of pAd-T34A also suppressed the growth of established tumours by 40%, and TUNEL staining of DNA fragmentation confirmed that this was due, at least in part, to apoptosis.

The debate over whether survivin is important for survival or cell division in higher organisms seems to be edging towards survival, but perhaps the most exciting prospects for cancer research are that, regardless of its function, survivin can be turned upon itself to block tumour growth.

Emma Greenwood

References and links

ORIGINAL RESEARCH PAPER Grossman, D. *et al*. Transgenic expression of survivin in keratinocytes counteracts UVB-induced apoptosis and cooperates with loss of p53. *J. Clin. Invest.* **108**, 991–999 (2001) | Mesri, M. *et al.* Cancer gene therapy using a survivin mutant adenovirus. *J. Clin. Invest.* **108**, 981–990 (2001)

FURTHER READING Reed, J. C. The survivin saga goes *in vivo*. *J. Clin. Invest.* **108**, 965–969 (2001)

TRIAL WATCH

Lymphoma reduction in HAART recipients

HIV infection is associated with a high incidence of non-Hodgkin's lymphoma. Since the mid-1990s, when highly active antiretroviral therapy (HAART) became widely used to treat HIV infection, the incidence of AIDS-related illnesses has decreased, leading to increased survival of AIDS patients. The effects of HAART on AIDS-related lymphomas, however, have been controversial. Besson *et al.* set out to settle this debate by comparing large data sets of HIV-positive lymphoma patients before and after the use of HAART. They found that between the early and late 1990s, the number of AIDS-related lymphoma cases decreased by 50%. Importantly, the incidence of primary brain lymphoma dropped almost threefold during these years. The prognosis for AIDS-related lymphoma has also improved. Besson *et al.* associate the reduced risk of lymphoma with the higher number of $CD4^+$ T cells observed in patients treated with HAART.

ORIGINAL RESEARCH PAPER Besson, C. *et al*. Changes in AIDS-related lymphoma since the era of highly active antiretroviral therapy. *Blood* **98**, 2339–2344 (2001)

Wave goodbye to radiotherapy?

Are women who receive radiotherapy for cancer in one breast at increased risk of developing cancer in the other breast? Lack of one *ATM* allele could affect the checkpoint response that allows repair of the damage inflicted by radiotherapy in normal breast cells, so women with *ATM* mutations might have an increased susceptibility to second cancers.

Fifteen groups worldwide plan to screen 700 women with bilateral breast cancer and 1400 women with unilateral breast cancer for mutations in the *ATM* gene. This study aims to uncover the role of *ATM* in women who develop bilateral breast cancer after radiatiotherapy for the initial breast tumour. The groups are using a mutation detection system called WAVE to identify *ATM* mutations in DNA samples taken from those participating in the trial. The results of this trial could influence the way that many women are treated for breast cancer in the future.

FURTHER READING Janin, N. *et al*. Breast cancer risk in ataxia telangiectasia (AT) heterozygotes: haplotype study in French AT families. *Br. J. Cancer* **80**, 1042–1045 (1999)

Glioma therapy on the right track

Established tumours nearly always contain necrotic cells, which can account for up to 50% of the tumour volume. A therapy that targets this necrotic core has just been awarded 'fast-track status' by the United States Food and Drug Administration, for the treatment of glioblastoma multiforme, in response to encouraging preliminary results in a Phase II clinical trial. The drug — Cotara™ (TNT-1/B) — is an ^{125}iodine-labelled antibody that targets the nucleosomal DNA released by necrotic cells. Once the antibody has found its target, β-radiation from the ^{125}iodine label kills the surrounding tumour cells. As more cells die, the tumour becomes an ever-more effective target for the antibody. A Phase III trial is planned for the end of the year.

WEB SITES

Phase II trial of Cotara: http://clinicaltrials.gov/ct/gui/c/w1b/show/NCT00004017