— which is responsible for the inactivation of caspase-3 and caspase-7 — and reversed caspase inhibition. (XIAP also suppresses an upstream initiator caspase-9 through the BIR3 region, but the authors decided to target a more downstream mechanism.)

The most active of these compounds induced apoptosis in a range of tumour cell lines and primary leukaemia cells *in vitro*, but showed little toxicity in normal cells. These compounds also sensitized tumour cells to the anticancer treatments etoposide, doxorubicin and paclitaxel. Inactive structural analogues had no effect on these tumour cells.

The induction of cell death by the XIAP antagonists was blocked by the universal caspase inhibitor zVAD-fmk and was reduced by overexpressing XIAP. Cell death was unaffected, however, by overexpression of the upstream apoptosis suppressors BCL-X_L and CRMA, which shows that targeting such a distal point in the apoptosis pathway bypasses many upstream defects in apoptosis-regulatory mechanisms in tumours. Delivered at modest doses, the XIAP antagonists also suppressed growth of established tumours in mouse xenograft models, with little toxicity to normal cells.

The results indicate that tumours have an intrinsic drive to activate caspases, and that inhibition of IAPs allows apoptosis to occur in tumours with little or a lesser effect in normal cells. The compatibility of XIAP antagonists with established anticancer drugs, and their ability to suppress tumour growth *in vivo*, provides a rationale to investigate pharmacokinetic and toxicological profiles for these compounds as single agents or as combined therapy.

Simon Frantz, Associate Editor (News),
Nature Reviews Drug Discovery

References and links

ORIGINAL RESEARCH PAPER Schimmer, A. D. *et al.* Small-molecule antagonists of apoptosis suppressor XIAP exhibit broad antitumor activity. *Cancer Cell* **5**, 25–35 (2004)
FURTHER READING Reed, J. C. Apoptosis-based therapies. *Nature Rev. Drug Discov.* **1**, 111–121 (2002) | Salvesen, G. S. & Duckett, C. S. IAP proteins: blocking the road to death's door. *Nature Rev. Mol. Cell Biol.* **3**, 401–410 (2002)

expression of proteins such as c-Myc, Waf1 and Kip1 that lead to uncontrolled proliferation. In support of this, the overexpression of c-Myc was shown to co-localize with that of active c-Met in epithelial cells.

So, it seems that in addition to its well-known influence on tumorigenic processes in cells in which it acts directly, Tgf-β also functions as an indirect suppressor of epithelial tumorigenesis through its effects on neighbouring fibroblasts. The question of why the effects of loss of Tgf-β signalling were seen in the prostate and forestomach, but not in other organs, remains to be investigated.

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References and links

ORIGINAL RESEARCH PAPER Bhowmick, N. A. *et al.* TGF-β signaling in fibroblasts modulates the oncogenic potential of adjacent epithelia. *Science* **303**, 848–851 (2004)
FURTHER READING Siegel, P. M. & Massagué, J. Cytostatic and apoptotic actions of TGF-β in homeostasis and cancer. *Nature Rev. Cancer* **3**, 807–820 (2003)

IN BRIEF

EARLY DETECTION

Visualization of tumors and metastases in live animals with bacteria and vaccinia virus encoding light-emitting proteins.

Yu, Y. A. *et al. Nature Biotechnol.* 8 Feb 2004 (doi:10.1038/nbt941)

Yu *et al.* show that microorganisms can preferentially survive and replicate in tumours. Bacteria and vaccinia virus engineered to express green fluorescent protein were visualized by real-time imaging in tumour-bearing rodents. Two days after injection, light emission was only observed in tumours and metastases, and after 45 days was still present in the primary tumour. So, microorganisms might be useful for cancer detection and treatment.

METASTASIS

Treatment of terminal peritoneal carcinomatosis by a transducible p53-activating peptide.

Snyder, E. L., Meade, B. R., Saenz, C. C. & Dowdy, S. F. *PLoS Biol.* **2**, 1–8 (2004)

Metastatic disease is difficult to treat. An alternative to gene therapy is systemic delivery of tumour suppressors. This approach is also limited, however, as the large proteins cannot cross the plasma membrane. Snyder *et al.* have delivered a p53-activating peptide to mice with terminal metastatic disease using peptides containing a protein transduction domain. p53 was activated in cancer cells, but not normal cells, and resulted in increased lifespan and disease-free animals.

THERAPEUTICS

Application of gene expression-based high-throughput screening (GE-HTS) to leukemia differentiation.

Stegmaier, K. *et al. Nature Genet.* 8 Feb 2004 (doi:10.1038/ng1305)

Stegmaier *et al.* developed GE-HTS as a cell-based approach to screen chemical libraries for compounds that regulate biological processes. They used GE-HTS to identify compounds that cause differentiation of acute myeloid leukeamia (AML) cells. Of the 1,739 compounds screened, 8 induced the GE-HTS AML differentiation signature and could induce at least one hallmark of differentiation assayed by conventional methods. This approach will be useful for dissecting the mechanisms that regulate AML differentiation.

IMMUNOTHERAPY

High vaccination efficiency of low-affinity epitopes in antitumor immunotherapy.

Gross, D.-A. *et al. J. Clin. Invest.* **113**, 425–433 (2004)

Cancer vaccines should help the immune system to recognize tumour cells. But, most tumour-associated antigens — which are used to make the vaccines — are also expressed on normal cells and cause autoimmunity to develop. Gross *et al.* report that low-affinity epitopes of TERT, a protein preferentially expressed in cancer cells, induce tumour immunity without causing autoimmunity. So, selection of low-affinity epitopes might overcome the problems associated with existing cancer vaccines.