WEB WATCH

COSMIC collection

- http://www.sanger.ac.uk/perl/CGP/cosmic

Somatic mutations in more than 260 genes have been identified from studies of human cancers, and a huge amount of data has been generated from this work. Rather than researchers spending hours carrying out literature searches or visiting various specialist databases, a single, comprehensive source of information on cancer-related somatic mutations would clearly be a good thing. In response to this need, the Cancer Genome Project, based at The Wellcome Trust Sanger Institute, launched a new web site on 4 February 2004. COSMIC (Catalogue of Somatic Mutations in Cancer) will bring these data together in one accessible, freely available resource.

COSMIC allows researchers to select their gene of interest and displays a map of where mutations occur in the amino-acid sequence. It also gives structural and functional information on protein domains and provides a list of samples containing each mutation, as well as a comprehensive list of publications for each altered site. Information can alternatively be accessed starting with tissue type, so that data are displayed for the genes that are mutated in each tissue. Data of interest can be exported in several useful formats, including text, HTML and Microsoft Excel spreadsheets.

The COSMIC web site will eventually contain data on all genes that are associated with human cancer. So far, details for four of these — *BRAF*, *HRAS*, *KRAS2* and *NRAS* — have been catalogued. This already provides data on 57,444 tumours and 10,647 mutations, giving an idea of the huge amount of information this project will eventually bring together.

Louisa Flintoft

THERAPEUTICS

Overcoming inhibition

Ever since resistance to apoptosis emerged as an influential pathway in cancer, targeting the mechanisms that allow tumours to avoid the same fate as normal cells has been proposed as a potent anticancer strategy. In *Cancer Cell*, John Reed and colleagues validate this principle by describing how small-molecule inhibitors that remove an important 'brake' in apoptosis can strip tumours of their immortality.

The ultimate effectors of programmed cell death are the caspase family of proteases. Normally, caspases are kept in check by members of the inhibitor of apoptosis (IAP) family, which bind to and inactivate caspases until they are needed. Caspases are overexpressed in tumours, but so are IAPs, and, therefore, failure to activate caspases could create resistance to apoptosis.

So, Reed and colleagues screened a library of around one million compounds for binding to one of the best characterized of the IAPs: XIAP. XIAP inhibits apoptosis at a distal step in the apoptosis pathway — at the convergence of cell-death pathways that are activated by mitochondria-dependent and mitochondria-independent stimuli.

Eight polyphenylurea-based compounds were identified that bind to the BIR2 domain of XIAP

TUMORIGENESIS

Nuisance neighbours

Disruptive neighbours can cause turmoil in any community and, in cancer, abnormal changes in one cell type can lead to tumorigenesis in other nearby cells. Reporting in *Science*, Harold Moses and colleagues now describe a new mechanism for this, showing that loss of transforming growth factor-β (TGF-β) signalling in stromal fibroblasts leads to oncogenic changes in adjacent epithelial cells.

It is well known that disrupting the normal interactions between epithelial cells and fibroblasts in the underlying stroma can lead to tumorigenesis, but the signalling pathways that are involved in this are poorly understood. To investigate a potential role of Tgf-β signalling in stroma–epithelium interactions, Moses and co-workers made transgenic mice in which the gene encoding the Tgf-β type II receptor (Tgf-βRII) — a crucial component of Tgf-β signalling — is specifically inactivated in fibroblasts (*Tgfbr2*^{fspKO} mice). Increased proliferation of both fibroblasts and epithelial cells was seen in prostate tissue from these mice, with prostate epithelial cells also showing neoplastic characteristics. In the forestomach, even more marked effects on epithelial cells were seen, with invasive squamous-cell carcinomas developing in 100% of *Tgfbr2*^{fspKO} mice.

But how does loss of Tgf-β signalling in fibroblasts trigger tumorigenesis in adjacent epithelia? Hepatocyte growth factor (Hgf) is one target of Tgf-β signalling, so Moses and colleagues analysed Hgf signalling in *Tgfbr2*^{fspKO} animals. Cultured fibroblasts from *Tgfbr2*^{fspKO} mice were found to secrete three times more of the active form of Hgf than cells from control mice. Furthermore, increased levels of the phosphorylated, active form of the Hgf receptor — c-Met — were seen in prostate and forestomach epithelial cells from *Tgfbr2*^{fspKO} mice.

The authors also showed increased expression of the tumour promoter c-Myc and decreased levels of the cyclin-dependent kinase inhibitors Waf1 and Kip1 in prostate and forestomach tissue from *Tgfbr2*^{fspKO} mice. This indicates that when Tgf-β signalling is disrupted in fibroblasts, increased Hgf signalling in neighbouring cells might lead to changes in the

— 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.

Louisa Flintoft

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.