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