found that almost all of them had sequence homology to known genes, mRNAs or expressed sequence tags. Examples include *Slit2* — which is epigenetically silenced in several human tumours — and *Nr4a3* — which is thought to be involved in T-cell apotosis and malignant chrondrosarcomas. In addition, for at least five of the cloned genes tested, promoter methylation was strongly correlated with reduced gene expression in mouse leukaemia cell lines. When the cell line under study was treated with a demethylating agent, gene expression was restored.

Another gene that the researchers found to be consistently silenced in the leukaemic mice was inhibitor of DNA binding 4 (*Idb4*). The function of IDB4 is not known, but they found that the human homologue, *ID4*, is silenced in over 85% of acute leukaemias and in 100% of chronic lymphocytic leukaemias. *ID4* is silenced much less frequently (~20%) in solid tumours, indicating that this effect is relatively selective for haematological malignancies. Plass, Caligiuri and colleagues showed that the transfection of (unmethylated) *Idb4* into mouse tumour cells increases apoptosis and slows their *in vivo* and *in vitro* growth, leading the researchers to suggest that *Idb4* is a tumour suppressor.

The next experiment will be to downregulate *Idb4* expression in a tumour cell line using small interfering RNA — although, in fact, the silencing of *Idb4* in tumours is so consistent that a leukaemic cell line expressing it has not yet been found. The apparent prevalance of epigenetic silencing in human leukaemia, and the demonstration that it can be reversed using demethylating agents, led the authors to conclude that as a putative tumour suppressor, *Idb4* is a potential biomarker, prognostic indicator and therapeutic target.

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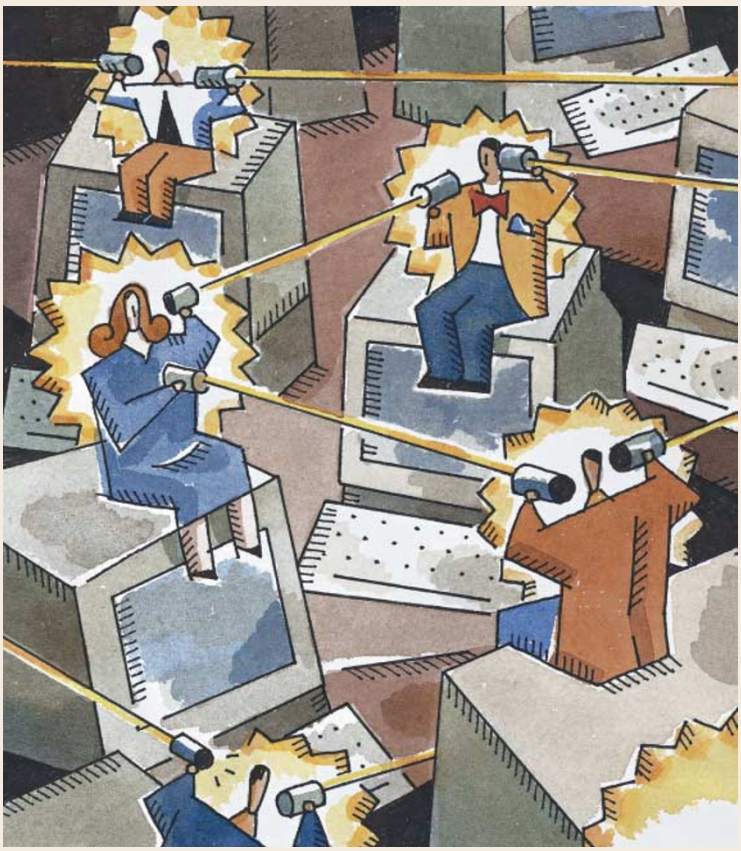
References and links

ORIGINAL RESEARCH PAPER Yu, L. *et al.* Global assessment of promoter methylation in a murine model of cancer identifies *ID4* as a putative novel tumor suppressor gene in human leukaemia. *Nature Genet.* 20 Feb 2005 (doi:10.1038/nrg1521)



IN BRIEF

THERAPEUTICS

Inhibition of indoleamine 2,3-dioxygenase, an immunoregulatory target of the cancer suppression gene *Bin1*, potentiates cancer chemotherapy.

Muller, A. J., DuHadaway, J. B., Donover, S., Sutanto-Ward, E. & Prendergast, G. C. *Nature Med.* 13 Feb 2005 (doi:10.1038/nm1996)

Increased expression of the immunomodulatory enzyme indoleamine 2,3-dioxygenase (IDO) mediates T-cell-mediated immune escape in tumour cells. Muller *et al.* report that IDO expression is regulated by the signalling protein BIN1 — tumours grown in *Bin1*-null mice are resistant to T-cell-mediated immunity. In a mouse model of breast cancer, the authors show that small-molecule inhibitors of IDO cooperate with cytotoxic agents to induce regression of established tumours.

VIRAL ONCOGENESIS

The Kaposin protein of KSHV activates the p38/MK2 pathway and stabilizes cytokine mRNAs.

McCormick, C. & Ganem, D. *Science* **307**, 739–741 (2005)

Cytokine production is an important factor in Kaposi's sarcoma herpesvirus (KSHV)-associated tumour progression. McCormick and Ganem show that Kaposin, a latent KSHV gene product, increases cytokine production by stabilizing the mRNAs that encode them. These findings reveal a new mechanism by which viruses can selectively modulate mRNA turnover and mediate tumorigenesis.

TUMOUR PROGRESSION

Succinate links TCA cycle dysfunction to oncogenesis by inhibiting HIF-α prolyl hydroxylase.

Selak, M. A. *et al. Cancer Cell* **7**, 77–85 (2005)

Succinate dehydrogenase (SDH) is a mitochondrial tricarboxylic acid (TCA)-cycle enzyme. Loss of SDH activity or expression is associated with renal-cell, gastric and colon cancers. Selak *et al.* show that SDH downregulation leads to the accumulation of succinate, a TCA-cycle metabolite, in the cytosol. There, succinate inhibits the hypoxia-inducible factor-1α (HIF1α) prolyl hydroxylase, resulting in HIF1α stabilization under normoxic conditions. This leads to increased expression of genes that promote tumour angiogenesis, metastasis and glycolysis.

GENETICS

The BRCA2 homologue Brh2 nucleates RAD51 filament formation at a dsDNA–ssDNA junction.

Yang, H., Li, Q., Fan, J., Hollman, W. K. & Pavletich, N. P. *Nature* **433**, 653–657 (2005)

Yang *et al.* describe the function of BRH2, a homologue of the tumour suppresssor BRCA2. They explain how BRH2 recruits the repair protein RAD51 to repair double-stranded DNA breaks. BRH1 acts preferentially at a junction between double-stranded and single-stranded DNA, and the authors propose that defects in this activity might lead to loss of the DNA-repair capacity of BRCA2-associated tumours.