ONCOGENES

Finding a PIG in a haystack

The chromosome region 20q11–13 is frequently amplified in human cancers, particularly in bladder cancer. It has been a challenge, however, to identify a cancer-causing gene among the many other genes at this locus. Guo *et al*. have finally found a new oncogene in this region — *CDC91L1* encodes the transamidase-complex protein PIG-U, which seems to contribute to human bladder cancer pathogenesis.

Guo *et al.* began their study by analysing a proband of patients with familial urothelial carcinoma that was associated with the germline translocation t(5;20)(p15;q11) — this translocation occurs at the 20q11–13 locus. The authors hoped that by isolating the translocation breakpoint, they could find a putative oncogene nearby. Shotgun cloning led to the identification of four genes that seemed to be affected by the translocation.

The authors analysed the expression levels of these genes in bladder cells taken from the proband, compared with normal individuals. They found that one of these — *CDC91L1* — was overexpressed fivefold in the uroepithelial cells from the patients with bladder cancer, making it a good candidate for a cancer-associated gene. Furthermore, the t(5;20)(p15;q11) breakpoint lies in the promoter region of *CDC91L1*, so the translocation is likely to induce its upregulation. Guo and colleagues screened various bladder cancer cell lines and primary tumour samples, and found that *CDC91L1* was overexpressed in over 30% of these. This is a much higher incidence than any other mutations that have been associated with bladder cancer.

But what happens when normal cells overexpress *CDC91L1*? Guo *et al.* showed that cells transfected with this gene grew at a faster rate and had increased anchorage-independent growth capability, compared with control cells. They also initiated tumour formation in nude mice. So *CDC91L1* is indeed an oncogene.

Further studies are required to determine exactly how PIG-U contributes to cellular transformation. In yeast, PIG-U is a subunit of a glycosylphosphatidylinositol (GPI) transamidase complex — enzymes that add a GPI anchor to membrane-associated proteins. Other transamidase genes have been found to be amplified in different tumour types, and the authors observed that *CDC91L1* overexpression led to the overproduction of several GPI-anchored proteins, including the urokinase receptor uPAR, in different cell types. Previous studies have shown that uPAR upregulation is associated with JAK–STAT signalling, and Guo *et al.* observed that STAT phosphorylation was increased in cells that overexpressed *CDC91L1*. So, targeting this oncogene might be a new way to shut down this oncogenic signalling pathway.

Kristine Novak

References and links

ORIGINAL RESEARCH PAPER Guo, Z. *et al*. *CDC91L1* (PIG-U) is a newly discovered oncogene in human bladder cancer. *Nature Med.* **10**, 374–381 (2004)

FURTHER READING Yu, H. & Jove, R. The STATs of cancer — new molecular targets come of age. *Nature Rev. Cancer* **4**, 97–105 (2004)

WEB SITE

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http://urology.jhu.edu/faculty/sidransky/index.html

IN BRIEF

ONCOGENES

High frequency of mutations of the *PIK3CA* gene in human cancers.

Samuels, Y. *et al*. *Science* 11 Mar 2004 (doi:10.1126/science.1096502)

Phosphatidylinositol 3-kinases (PI3Ks) are lipid kinases that regulate signalling pathways involved in proliferation, survival and motility. To determine if they are mutated in cancer cells, Samuels *et al*. sequenced PI3K genes in hundreds of tumour samples and found that *PIK3CA*, which encodes the p110α catalytic subunit, is mutated in many colon, brain, gastric, breast and lung cancers. *PIK3CA* is therefore likely to be an oncogene that might be of use for early detection, prognosis or as a therapeutic target.

CARCINOGENESIS

The stroma as a crucial target in rat mammary gland carcinogenesis.

Maffini, M. V. *et al. J. Cell Sci.* **117**, 1495–1502 (2004)

Carcinogens can cause mutations in epithelial cells and can alter epithelial–stromal cell interactions, but which process is important for tumour formation? Using a rat mammary-tissue-recombination model and *N*-nitrosomethylurea (NMU), Maffini *et al*. showed that stromal cells exposed to NMU *in vitro* can transform normal mammary epithelial cells *in vivo*, whereas NMU-treated epithelial cells form normal ducts *in vivo*. This work indicates that the stroma is an important target of carcinogens.

IMMUNOTHERAPY

Immunoprevention of basal cell carcinomas with recombinant hedgehog-interacting protein.

Vogt, A. *et al. J. Exp. Med.* **199**, 753–761 (2004)

Abnormal hedgehog signalling causes basal-cell carcinomas (BCCs). The authors found that hedgehog-interacting protein (Hip1) is overexpressed in BCCs in the $Ptch^{+/-}$ mouse model of this disease. $Ptch^{+/-}$ mice immunized with Hip1 polypeptides produce effective B-cell and T-cell immune responses that reduce the number of BCCs. Immunization with proteins that are upregulated by the hedgehog pathway could therefore prevent BCCs in people who are genetically predisposed to developing this type of tumour.

TUMORIGENESIS

Epigenetic differences between Wilms' tumour in white and east-Asian children.

Fukuzawa, R. *et al. Lancet* **363**, 446–451 (2004)

Asian children who develop Wilms' tumours are younger than children of other races and are predominantly male. Imprinting of the maternal insulin-like growth-factor gene (*IGF2*) is lost in some Wilms' tumours, so the authors investigated whether the frequency of this loss of imprinting (LOI) explains these interethnic differences. *IGF2* LOI and associated precancerous lesions occur at a low frequency in children of east-Asian origin and a high frequency in Caucasian children, indicating that tumorigenesis is occurring by two distinct mechanisms.