tumour of origin. But the classifier fared less well on poorly differentiated (high-grade) carcinomas, indicating that their gene-expression patterns are fundamentally different from those of well-differentiated tumours from the same tissue. Might this reflect a different cellular origin for these tumours? Perhaps it's time to refine our tumour classification systems to take these differences into account.

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References and links

ORIGINAL RESEARCH PAPER Ramaswamy, S. *et al.* Multiclass cancer diagnosis using tumor gene expression signatures. *Proc. Natl Acad. Sci. USA* **98**, 15149–15154 (2001)

FURTHER READING Su, A. I. *et al*. Molecular classification of human carcinomas by use of gene expression signatures. *Cancer Res*. **61**, 7388–7393 (2001)

WEB SITES

Complete list of tumour marker genes:
http://www-genome.wi.mit.edu/MPR/GCM.html

SVM-FU algorithm software:
http://www.ai.mit.edu/projects/cbcl

APOPTOSIS

Drifting downstream

How many ways are there of blocking p53-mediated apoptosis? Many cancer cells avoid programmed cell death by inactivating p53 itself or one of its upstream regulators, but Fei Su and colleagues, in the January issue of *Genes & Development*, describe an unusual oncogenic signalling pathway that inhibits the pathway downstream of p53.

The story begins with an oncogenic growth factor — called WNT-1-induced secreted protein 1 (WISP1) — that is overexpressed in 30–40% of human colon cancers. WISP-1 belongs to a family of growth factors known as the CCN family, some members of which signal by binding to integrins rather than to classical receptor tyrosine kinases. One of the downstream targets of integrin-mediated signalling is the serine/threonine kinase AKT, a well-known promoter of cell survival. So does WISP-1 activate AKT? To find out, the authors treated cells with medium from cells that had been transfected with either *WISP1* or an empty vector. Western blots detected activated AKT, which is phosphorylated on serine 473, only in extracts from cells treated with the WISP1-conditioned medium. This activation was definitely caused by WISP1 because it was blocked by an antibody to WISP1. One of AKT's targets — glycogen synthase kinase 3β (GSK3β) — was also phosphorylated in response to WISP1-conditioned medium.

So does WISP1 block apoptosis by activating AKT? The authors treated cells with two DNA-damaging agents — etoposide and ultraviolet (UV) light — that activate the stress-mediated apoptotic pathway. Cells treated with WISP1-conditioned medium were protected from apoptosis mediated by these agents. Caspase-3 is an important 'effector' protease in the apoptotic pathway, but its activation by proteolytic processing was abrogated in cells treated with WISP1-conditioned medium. The caspase cascade is activated by the release of cytochrome *c* from mitochondria, which then binds and activates APAF1. Treatment with WISP1-conditioned medium also blocked cytochrome *c* release in response to etoposide or UV light. All these experiments were performed in cells that contain wild-type p53, but, in cells lacking p53, WISP1 was unable to prevent apoptosis induced by etoposide or UV light. There are two main apoptotic pathways: stress-activated apoptosis (such as that mediated by etoposide or UV light) is p53 dependent, whereas receptor-activated apoptosis (mediated by 'death receptors' such as FAS) is independent of p53 and APAF1. WISP1 seems to target the stress-activated pathway as it couldn't block apoptosis mediated by FAS.

So does WISP1 block stress-mediated apoptosis by disabling p53? Surprisingly, the answer to this question is no. p53 seemed to be activated normally in the presence of WISP1: three of p53's target genes — *MDM2*, *CDKN1A* and *BAX* — were upregulated in response to UV light or etoposide.

Is the WISP1-mediated blockade of p53-mediated apoptosis entirely dependent on AKT? This would make sense, as several of AKT's substrates are involved in regulating cytochrome-*c*-mediated apoptosis. Transfection with a kinase-dead mutant of AKT attenuated, but didn't completely block, the protective effect of WISP1, so the search was on for another anti-apoptotic mechanism that might be triggered by WISP1. The BCL-2 family of proteins regulate sensitivity to apoptosis by controlling the exit of cytochrome *c* from mitochondria. So the authors compared the levels of BCL-2 family members in WISP1-expressing and non-expressing cells, and found an increase in a single member of this family — the anti-apoptotic protein BCL-X_L.

So WISP1 seems to work downstream of p53, blocking cytochrome *c* release by activating both AKT and BCL-X_L. The gaps now need to be filled in by paddling back upstream from these two effectors of survival to WISP1's receptor.

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References and links

ORIGINAL RESEARCH PAPER Su, F. *et al.* WISP-1 attenuates p53-mediated apoptosis in response to DNA damage through activation of the Akt kinase. *Genes Dev.* **16**, 46–57 (2002)

WEB SITE

Arnold Levine's lab:
http://www.rockefeller.edu/labheads/levine/levine.html