cells (HUVECs) that were exposed to VEGF showed increased ILK activity. This was dependent on PI3K, as this effect was blocked by the addition of a PI3K inhibitor. Furthermore, inhibition of ILK function suppressed the migration and proliferation of HUVECs in response to VEGF. The authors also showed that ILK inhibitors block VEGF-stimulated angiogenesis in two standard assays.

A mouse xenograft model was used to test the effects of ILK inhibitors *in vivo*. Nude mice were injected with PC3 cells, and animals bearing well-established tumours were treated with an ILK inhibitor. Treated mice showed a reduced density of tumour-associated blood vessels and a decrease in tumour mass, as compared with untreated mice, and did not show any obvious side-effects. These results indicate that ILK, with its dual role in tumour angiogenesis, might prove to be a useful target for anticancer therapies.

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References and links

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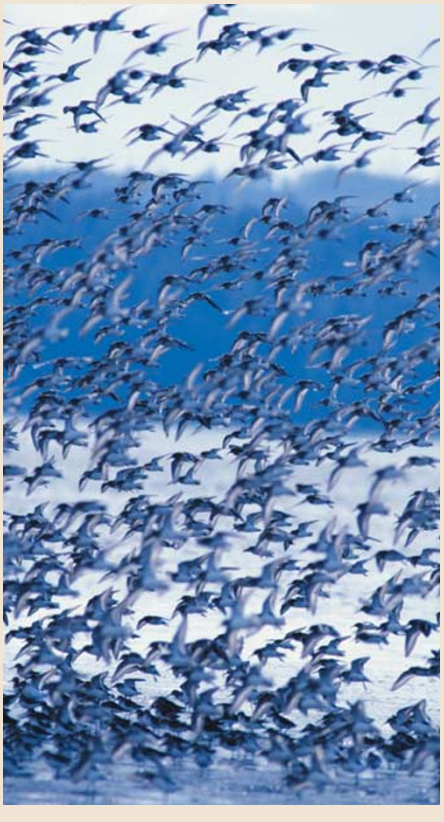

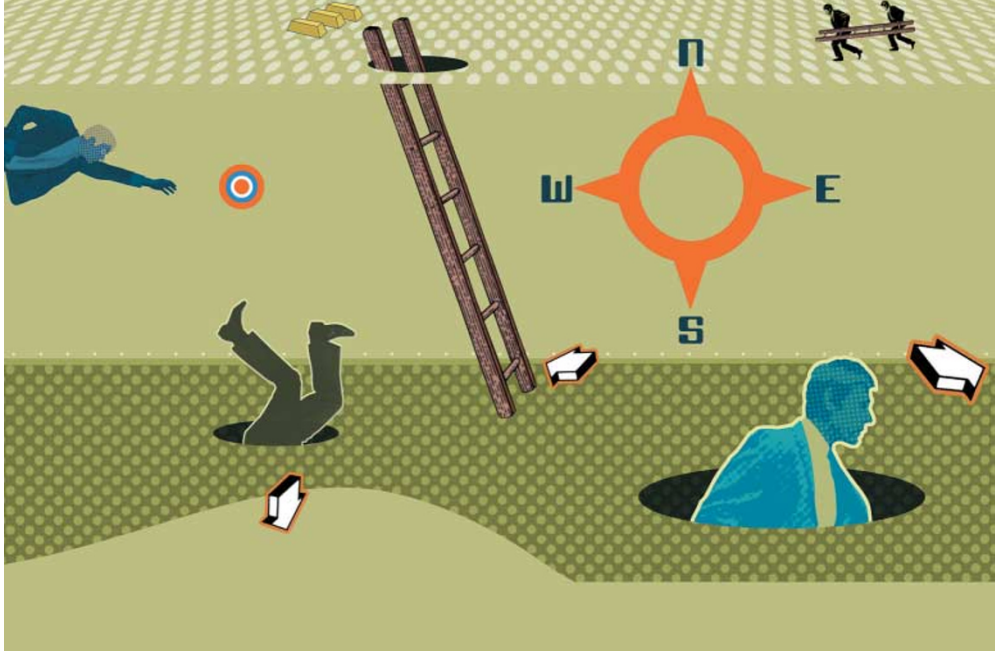

TUMOUR SUPPRESSORS

A topsy-turvy world

Tumour suppressors normally inhibit cell proliferation, but one seems to act in the opposite manner. Chun-Ming Chen and Richard Behringer report in the February issue of *Genes & Development* that it is the loss of OVCA1 that causes proliferation defects — only when its loss is combined with that of p53 is its tumour-suppressive activity unleashed.

The genes that cause ovarian cancer are largely unknown, so the identification of a region of chromosome 17 that is frequently lost was an important find. The *OVCA1* gene has since been shown to reside at that location, but it has yet to be shown to act as a tumour suppressor. The authors had previously identified the mouse orthologue, and continued their studies to understand the function of Ovca1.

They generated knockout mice, but these either died during development or shortly after birth. The embryos showed developmental defects and were generally smaller. Transplanting the ovaries into kidney capsules of wild-type mice allowed their development to be followed over time, and although smaller, development seemed normal and there was no evidence of carcinomas.

The growth defect could be caused by a decrease in proliferation or an increase in apoptosis, so *Ovca1*-null mouse embryonic fibroblasts (MEFs) were established to answer this question. The MEFs grew poorly, but there was no sub-G1 population, which would be indicative of apoptosis. Cell-cycle analysis revealed that fewer cells were in S phase, and this corresponded with a decrease in phosphorylated Rb, which would explain the inability of the cells to enter S phase.

But this is an unusual property for loss of a tumour suppressor, so might elimination of a checkpoint allow the cells to recover from this proliferation defect? The authors found that $Ovca1^{-/-}Trp53^{+/-}$ MEFs also had a reduced S-phase population, but $Ovca1^{-/-}Trp53^{-/-}$ MEFs grew normally. Loss of p53 could not rescue the developmental defects though — the mice still died soon after birth.

The next important question was whether Ovca1 actually did act as a tumour suppressor *in vivo*. Almost 60% of $Ovca1^{+/-}$ mice developed a range of tumours by two years, with an average latency of 92 weeks. This was shortened to 52 weeks in $Ovca1^{+/-}Trp53^{+/-}$ mice, and the incidence was increased to 72%. Importantly, the loss of one *Ovca1* allele increases the tumour incidence when compared with $Trp53^{+/-}$ mice, and although the tumour incidence in $Ovca1^{+/-}Trp53^{-/-}$ and $Trp53^{-/-}$ mice is the same, more mice have numerous tumours when they have lost one *Ovca1* allele. The tumour spectrum is also somewhat different in the *Ovca1* heterozygous mice.

So, despite its role as a positive regulator of cell-cycle progression, it seems that OVCA1 is, indeed, a tumour suppressor. Further work is needed to understand exactly how it functions in normal cells, and how its loss accelerates tumour progression when p53 is also lost.

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WEB SITE

Richard Behringer's lab:
http://www3.mdanderson.org/~genedev/behringer.html