MOUSE MODELS

A first for ovarian cancer

Ovarian cancer can be effectively treated if caught early, but it is generally diagnosed after it has metastasized. This has a serious impact on the survival of patients, and has also limited our knowledge of the early genetic changes that induce ovarian cancer. Sandra Orsulic *et al.*, reporting in the launch issue of *Cancer Cell*, have developed the first mouse model of ovarian cancer with defined genetic lesions, which should improve our understanding of cancer development.

Trp53$^{+/+}$ and *Trp53*$^{-/-}$ ovarian cells from transgenic mice that express an avian virus receptor were transfected *in vitro* with avian retroviral vectors carrying oncogenes that are frequently amplified or mutated in human ovarian cancer: *Kras2*, c-*Myc* and *Akt*. The authors investigated which combinations of genetic lesions could induce tumour formation *in vivo* by injecting these ovarian cells subcutaneously into nude mice and monitoring for tumour growth. Tumours arose only from cells that were deficient for *Trp53*, and had acquired at least two oncogenes by infection.

But can these cells also induce tumour growth at their natural site of formation: the ovaries? Implantation of infected cells under the ovarian capsule of nude mice results in ovarian tumours within 2 weeks. These metastasize to the same sites as human ovarian cancers within 4 weeks.

As the immune system might limit tumour growth in humans, the infected ovarian cells were also implanted under the ovarian capsule of the immunocompetent mice from which the cells were removed; ovarian tumours developed after three months.

This mouse model should help unravel the molecular basis of ovarian cancer development, and will provide a system for testing new therapeutic approaches.

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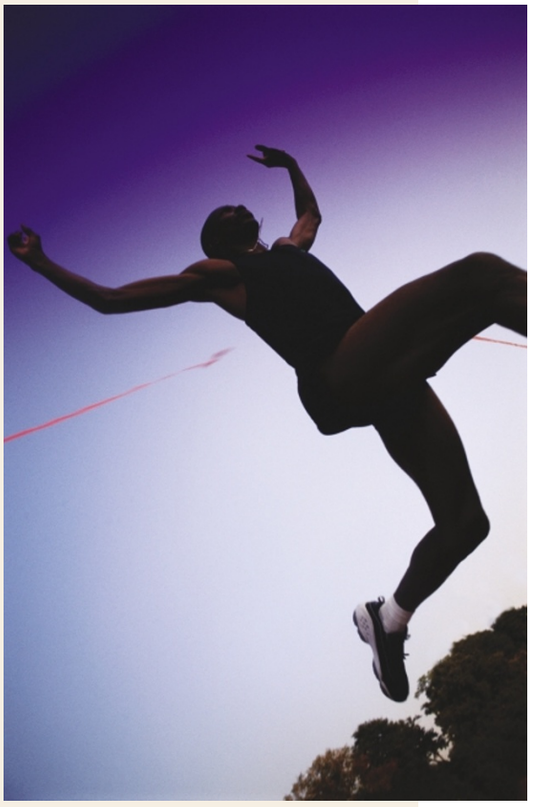

References and links

ORIGINAL RESEARCH PAPER Orsulic, S. *et al*. Induction of ovarian cancer by defined multiple genetic changes in a mouse model system. *Cancer Cell* **1**, 1–10 (2002)

WEB SITES

Harold Varmus's lab:
http://www.ski.edu/lab_homepage.cfm?lab=203

Encyclopedia of Life Sciences: http://www.els.net
human disease: mouse models

TUMOUR SUPPRESSORS

Keeping damage in check

Mutations in the tumour-suppressor gene *BRCA1* predispose individuals to breast and ovarian cancer. The protein has been assigned many functions though, so how does its deficiency contribute to tumorigenesis? Ronit Yarden *et al.* report in *Nature Genetics* that BRCA1 is involved in cell-cycle arrest following DNA damage, which allows cells time to repair their DNA.

The breast cancer cell line HCC1937 possesses just one copy of *BRCA1*, and this contains an inactivating mutation that is associated with an increased cancer risk. These cells are unable to arrest following γ-irradiation, but transfection with *BRCA1* restores this ability.

As cells arrest at the G2/M checkpoint by inhibiting the CDC2–cyclin-B kinase, Yarden *et al.* determined the protein levels and activity of CDC2–cyclin-B in HCC1937 cells and those transfected with *BRCA1*. Both expression of cyclin B1 and activity of the CDC2–cyclin-B kinase are decreased in *BRCA1*-expressing cells.

CDC2–cyclin-B activity is negatively regulated by the phosphorylation of CDC2's Tyr15 residue, so are the proteins that control Tyr15 phosphorylation also regulated by BRCA1? CDC25C, the activatory phosphatase, is down-regulated after irradiation in *BRCA1*-expressing cells, and this corresponds with an increase in the inhibitory kinase WEE1 and the level of phosphorylated CDC2-Tyr15. 14-3-3 proteins, which transport CDC25C from the nucleus following DNA damage to prevent activation of CDC2–cyclin-B, are also upregulated in *BRCA1*-expressing cells, and immunofluorescence revealed that CDC25C is, indeed, cytoplasmic in *BRCA1*-expressing cells.

But how does BRCA1 induce these effects? CHK1 and CHK2 are essential for the cell-cycle arrest in response to DNA damage, so might BRCA1 activate one of these checkpoint proteins? BRCA1 physically interacts with CHK1 and stimulates its activity after DNA damage. The G2/M arrest is also dependent on CHK1, as *BRCA1*-expressing cells that were treated with a CHK1 inhibitor lost the ability to induce this arrest.

BRCA1 therefore seems to be the link between the DNA-damage-sensing proteins ATM and ATR — which phosphorylate BRCA1 — and downstream members of the G2/M checkpoint pathway. So BRCA1 maintains genome stability by allowing cells time to repair their DNA following DNA damage. Only time will tell if it also inhibits tumorigenesis by other mechanisms.

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References and links

ORIGINAL RESEARCH PAPER Yarden, R. I. *et al*. BRCA1 regulates the G2/M checkpoint by activating Chk1 kinase upon DNA damage. *Nature Genet.* **30**, 285–289 (2002)

WEB SITE

Lawrence Brody's lab:
http://www.nhgri.nih.gov/Intramural_research/People/brody.htm