

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.

Emma Greenwood

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 Varnus'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.

Emma Greenwood

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