IN BRIEF

THERAPY

Inhibition of the c-Abl–TAp63 pathway protects mouse oocytes from chemotherapy-induced cell death

Gonfloni, S. *et al. Nature Med.* 27 Sep 2009 (doi:10.1038/nm.2033)

Loss of fertility after chemotherapy is a substantial problem for pre-menopausal cancer survivors. This paper indicates that the treatment of oocytes with cisplatin induces the phosphorylation and stabilization of the p53 family member TAp63 by the kinase ABL, and this induces the transcription of pro-apoptotic genes. Blocking the activity of ABL using imatinib prevented oocyte loss in female mice treated with cisplatin and helped to preserve fertility. Whether the systemic use of imatinib will also protect tumour cells from cisplatin treatment needs to be investigated.

SENESCENCE

SnoN functions as a tumour suppressor by inducing premature senescence

Pan, D., Zhu, Q. & Luo, K. *EMBO J.* 10 Sep 2009 (doi:10.1038/emboj.2009.250)

SNO-N, which is related to the oncoprotein SKI, can have pro-oncogenic functions owing to its capacity to repress transforming growth factor-β (TGFβ) signalling. However, this paper indicates that, independently of its function in the TGFβ pathway, SNO-N can limit tumorigenesis. SNO-N interacts with the promyelocytic leukaemia (PML) protein, and is recruited through this interaction to PML bodies. This results in the stabilization of p53, leading to premature senescence. Overexpression of SNO-N suppresses papilloma development in the skin of mice exposed to chemical carcinogens.

GENETICS

Expression of human BRCA1 variants in mouse ES cells allows functional analysis of *BRCA1* mutations

Chang, S. *et al. J. Clin. Invest.* 27 Sep 2009 (doi:10.1172/JCI39836)

Despite the fact that mutations in *BRCA1* are known to predispose to the development of breast and ovarian cancer, not all the mutations that occur in this gene have been characterized for their effect on protein function. This makes it difficult to give guidance to mutation carriers with variants of unknown clinical significance (VUS). This lack of genotype–phenotype information stems from a dearth of assays that identify how these different mutations affect protein function. Suhwan Chang and colleagues have used mouse embryonic stem (ES) cells to evaluate several VUS. Expression of wild-type *BRCA1* in *Brca1*-null ES cells rescues these cells, and other variants that enable ES cell survival were analysed for their effects on cell cycle regulation, differentiation and genomic stability. One VUS, S1497A, had an effect on genomic stability. ES cells expressing the S1497A variant were hypersensitive to γ-irradiation, primarily owing to reduced phosphorylation of this mutant BRCA1 that prevented recruitment to the sites of DNA damage. Interestingly, this mutant did not affect DNA repair through homologous recombination and had no effect on the response of cells to DNA-damaging drugs, indicating that the S1497A variant has a specific function in the repair of DNA damage that is induced by radiation, leading to increased genomic instability. The authors report that the effect of different variants can be established in less than 2 months using this approach.