GENOMIC INSTABILITY

# Two worlds collide

Fanconi's anaemia (FA) and ataxia telangiectasia (AT) are clinically distinct cancer-susceptibility syndromes that show defects in DNA repair. The components that are disrupted in either disorder were thought to function in separate DNA-damage pathways. Now, new research from Toshiyasu Taniguchi *et al.* shows that this is not so: a protein that was previously implicated in FA also functions in the AT pathway.

FA and AT cells are hypersensitive to cross-linking agents such as mitomycin C (MMC) and ionizing radiation (IR), respectively. AT cells carry mutations in ATM — a protein kinase that is required to orchestrate the S phase and G2/M checkpoints in response to IR. FA cells have defects in one of several proteins that operate in a common pathway: a nuclear complex of five FANC proteins (A, C, E, F and G) functions in response to MMC by triggering the addition of a ubiquitin molecule (mono-ubiquitylation) to FANCD2, in cooperation with the BRCA1 tumour suppressor. This modification localizes FANCD2 to nuclear foci that are thought to assemble at the sites of DNA damage. Cells that lack any of the FANC proteins, or contain a FANCD2 mutant that cannot be mono-ubiquitylated, cannot efficiently repair MMC-induced damage.

Taniguchi *et al.* now find that cells that lack FANCD2 have something in common with AT cells: unlike other FA cells, they have a defect in the IR-inducible S-phase checkpoint. The authors go on to show that FANCD2 is phosphorylated in response to IR but not MMC, and that the kinase responsible is ATM. The conserved S222 residue seems to be the most important phosphorylation site *in vivo*, and a FANCD2 mutant lacking S222 fails to restore IR-inducible activation of the S-phase checkpoint in cells that lack FANCD2. Interestingly, FANCD2 phosphorylation following IR does not require the presence of other FA proteins or its mono-ubiquitylation site — K651. This finding indicates that, although FANCD2 is mono-ubiquitylated in response to IR and localizes to nuclear foci, this is unlikely to be necessary for FANCD2's role in the response to IR.

So two distinct DNA-repair pathways can converge on FANCD2 and regulate its function through independent post-translational modifications. This model fits well with preliminary observations by the authors that patients with mutations in *FANCD2* seem to have more severe clinical phenotypes than AT patients or those with defects in other *FANC* genes. Future research into this exciting new link between FA and AT will no doubt focus on exactly how FANCD2 ubiquitylation and phosphorylation function in the two types of DNA damage.

*Barbara Marte*
*Editor,* Nature Cell Biology

**References and links**

**ORIGINAL RESEARCH PAPER** Taniguchi, T. *et al.* Convergence of the Fanconi anemia and ataxia telangiectasia signaling pathways. *Cell* **109**, 459–472 (2002)

**FURTHER READING** Garcia-Higuera, I. *et al.* Interaction of the Fanconi anemia proteins and BRCA1 in a common pathway. *Mol. Cell* **7**, 249–262 (2001)

# IN BRIEF

THERAPEUTICS

## Drug-induced ubiquitylation and degradation of ErbB receptor tyrosine kinases: implications for cancer therapy.

Citri, A. *et al. EMBO J.* **21**, 2407–2417 (2002)

The receptor tyrosine kinase *ERBB2* is overexpressed in many cancers, and is an important target for cancer treatment. Drugs that inhibit the kinase activity are proving effective, and Yosef Yarden and colleagues have shown that some tyrosine kinase inhibitors, notably CI-1033, also promote ubiquitylation, and hence degradation, of ERBB2, to further improve the efficacy of the drug.

TUMOUR SUPPRESSORS

## Expression of several genes in the human chromosome 3p21.3 homozygous deletion region by an adenovirus vector results in tumor suppressor activities *in vitro* and *in vivo*.

Ji, K. *et al. Cancer Res.* **62**, 2715–2720 (2002)

Deletions in the human chromosome 3p21.3 region have been associated with lung cancers, but the region contains more than 25 genes, making it difficult to determine which ones are tumour suppressors. Ji *et al.* used adenoviral vectors to assess the tumour-suppressive capability of each gene *in vitro*. *101F6, NPRL2* and *FUS1* induced human lung cancer cell-specific apoptosis, and their intratumoral injection suppressed lung cancer in mouse models.

ONCOGENES

## Amplification of PPM1D in human tumours abrogates p53 tumour suppressor activity.

Bulavin, D. V. *et al. Nature Genet.* **31**, 210–215 (2002)

## Oncogenic properties of PPM1D located within a breast cancer amplification epicentre at 17q23.

Li, J. *et al. Nature Genet.* **31**, 133–134 (2002)

In response to oncogenic RAS activation, p38 mitogen-activated protein kinase can phosphorylate and activate p53. The phosphatase PPM1D — which is amplified in 11% of human breast tumours — blocks this phosphorylation and prevents the senescence response that protects cells from the oncogenic effects of RAS.

THERAPEUTICS

## Targeting Raf-1 gene expression by a DNA enzyme inhibits juvenile myelomonocytic leukaemia cell growth.

Iversen. P. E. *et al. Blood* **99**, 4147–4153 (2002)

Children with juvenile myelomonocytic leukaemia (JMML) are resistant to standard chemotherapy. A potential therapeutic strategy for JMML has been developed that blocks an autocrine loop: cytokines activate the RAS–RAF–mitogen-activated protein kinase (MAPK) pathway and cause JMML cells to secrete more cytokines. A DNA enzyme that specifically cleaves *RAF1* mRNA blocked cytokine production in JMML cells but had no effect on normal bone-marrow cells. Continuous infusion of the enzyme prevented the growth of JMML cells in immunodeficient mice.