the inactivation of DIAP1 is a critical event in potentiating cell death, as under normal circumstances, DIAP1 mediates the ubiquitination and, most likely, the degradation of Dronc, thus preventing the initiation of a caspase cascade (Fig. 1b). Although these papers provide great insight into cell death in *Drosophila*, they also pose new questions. For example, the observation that Reaper and Grim can repress translation is a fascinating, but how is this achieved? A hidden message in these papers is that context is very important; it is apparent that Reaper and Grim differ from Hid in how they mediate degradation of the IAPs, but it also is obvious that cellular context is important. Another question that emerges from these reports is whether Morgue-induced ubiquitination of IAP functions independently of, or in conjunction with, Reaper and Grim. Finally, an obvious question is whether Smac/Diablo and/or Omi/HtrA2 function in a similar fashion to Reaper, Grim and Hid and are, therefore, responsible for the ubiquitination of IAPs in mammalian cells. It is clear that these exciting reports provide the impetus for many new avenues of future research. □

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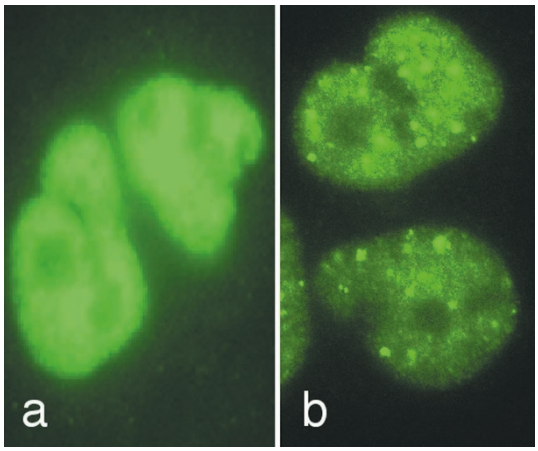
A FANCy double life

Fanconi's anaemia (FA) and ataxia–telangiectasia (AT) are autosomal recessive, clinically distinct cancer-susceptibility syndromes; patients have defective DNA-repair systems. The components disrupted in these disorders were thought to function in separate DNA-damage repair pathways, but new research from Taniguchi *et al.* (*Cell* **109,** 459–472; 2002) shows that this is not so. The FANCD2 protein, which was previously implicated in FA, is also involved 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 have mutations in the ATM kinase, which is normally activated in response to IR and required for the IR-inducible S phase and G2/M checkpoints. FA cells have defects in one of several FA proteins, all of which operate in the same pathway. A nuclear complex of five FA (FANC) proteins (A, C, E, F and G) responds to MMC by triggering the monoubiquitination of FANCD2. This modification results in FANCD2 being localized to nuclear foci that are thought to assemble at the sites of DNA damage. Cells that lack any one of the FA proteins or contain a FANCD2 mutant that cannot be ubiquitinated are unable to efficiently repair MMC-induced damage.

Taniguchi *et al.* now find that, unlike other FA cells, those that lack FANCD2 (D2) are not only sensitive to MMC, but, similar to AT cells, they also have a problem with their IR-inducible S-phase checkpoint. The authors go on to show that FANCD2 is phosphorylated in response to IR, but not MMC, and that ATM is the kinase responsible. The conserved Ser222 residue seems to be the most critical phosphorylation site *in vivo*, and a FANCD2 mutant that lacks Ser222 fails to restore IR-inducible activation of the S-phase checkpoint in D2 cells. Interestingly, FANCD2 phosphorylation after exposure to IR does not require other FA proteins or its monoubiquitination site Lys651 (left panel, localization of the Lys651→Arg mutant in response to IR). This finding suggests that, although FANCD2 is monoubiquitinated in response to IR and localizes to nuclear foci (right panel, wild-type FANCD2 localization in response to IR), this is probably not required for FANCD2's involvement in the IR response.



TOSHIYASU TANIGUCHI AND ALAN D'ANDREA

So FANCD2 leads a double life, and two distinct DNA-repair pathways converge on it 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 FA genes. Future research into this exciting new link between FA and AT will no doubt focus on how exactly ubiquitination and phosphorylation of FANCD2 function in the two types of DNA damage repair.

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