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URLs

FANCI
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&md=Retrieve&dopt=full_report&list_uids=55215

FANCD2

<http://ca.expasy.org/uniprot/Q9BXW9>

Fanconi anaemia (FA) is a chromosome instability and development disorder that falls into 13 complementation groups, 12 of which have been linked to distinct genes. However, the FA-I complementation group has remained uncharacterized. Several new studies report the identification of new factors — including the protein associated with the FA-I group — that are crucial for the FA-associated DNA-damage response.

Using a proteomics screen for DNA-damage-induced phosphorylation substrates of ATM and ATR kinases (which regulate the FA-mediated DNA-repair pathway) coupled with a genetic screen for DNA-damage sensitivity, Smogorzewska *et al.* identified an uncharacterized protein, KIAA1794, which confers resistance to a DNA-crosslinking agent (mitomycin C; MMC). They showed that the corresponding gene matched the FA-I complementation group and was hence renamed **FANCI**. Knockdown of **FANCI** in the presence of MMC resulted in cytogenetic abnormalities and hypersensitivity, defective G2–M and intra-S-phase checkpoints, and reduced homologous recombination following DNA double-strand breaks — which are all typical cellular features in patients with FA. Moreover, **FANCI** localized to DNA-damage-induced nuclear foci and colocalized with **FANCD2**.

FANCD2 is monoubiquitylated by the FA core complex, which consists of eight FA proteins and has E3 ubiquitin ligase activity. Sims *et al.* carried out a **FANCD2**-based sequence homology search and identified **FANCI** as a potential substrate. Both studies

showed that **FANCI** is monoubiquitylated in a DNA-damage-inducible manner by the FA core complex, and that **FANCI** monoubiquitylation is important for its recruitment to damage-induced nuclear foci. Surprisingly, the monoubiquitylation of **FANCI** also depended on the presence of **FANCD2**. This relationship

“The reciprocal ubiquitylation dependency between **FANCD2** and **FANCI** is also puzzling. But their physiological significance is real...”

is reciprocal, because depletion of **FANCI** resulted in diminished ubiquitylation of **FANCD2** and a reduction in **FANCD2** levels. There is evidence that **FANCI** and **FANCD2** form a complex, but it is not clear whether the effect of **FANCI** knockdown on **FANCD2** protein stability is due to the loss of this interaction. The reciprocal ubiquitylation dependency between **FANCD2** and **FANCI** is also puzzling. But their physiological significance is real: Smogorzewska *et al.* were able to complement three FA phenotypes (MMC hypersensitivity, failure to monoubiquitylate **FANCD2**, and chromosome breakage) in **FANCI**-defective cells with retrovirally expressed **FANCI**. Supporting the biochemical characterization of **FANCI**, Dorsman *et al.* studied FA-I families using a classic genetic linkage analysis approach and

found a candidate gene (**KIAA1794**) that was mutated in eight patients and which they subsequently identified as **FANCI**.

Finally, Ling *et al.* identified a new component of the FA core complex, the 100-kDa polypeptide **FAAP100**, by mass spectrometry. **FAAP100** forms a stable subcomplex with **FANCL** and **FANCB** that can be biochemically purified. Assembly of the subcomplex stabilizes the components and protects them against degradation. Nuclear localization of the subcomplex is regulated by other components of the FA core complex. **FAAP100** is essential for the stability of the FA core complex and for monoubiquitylation of its crucial substrate, **FANCD2**. In addition, **FAAP100**-knockout cells display the hallmarks of FA but, so far, no **FAAP100** mutations have been identified in patients with FA. The authors propose that the FA core complex consists of multiple subcomplexes, the biochemical purification of which could eventually allow reconstitution of the full complex.

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FURTHER READING Huang, T. T. & D'Andrea, A. D. Regulation of DNA repair by ubiquitylation. *Nature Rev. Mol. Cell Biol.* **7**, 323–334 (2006)