DNA DAMAGE RESPONSE

Bridging genomic instability disorders

A link between Fanconi anaemia and Bloom's syndrome, two genome instability disorders with similar phenotypes, has been identified. The proteins encoded by the causal genes of both syndromes interact following interstrand cross link (ICL) formation, and this is mediated by FANCM, the only Fanconi anaemia core protein known to have intrinsic DNA-binding activity.

Two evolutionarily conserved motifs in FANCM, MM1 and MM2, were identified that interact with the Fanconi anaemia core protein FANCF and the Bloom's syndrome proteins RM11 and topoisomerase IIIα, respectively. Loss of FANCM by small interfering RNA prevented the association of FANCF (and other Fanconi anaemia core proteins) with Bloom's syndrome proteins, confirming that FANCM links the two protein complexes. Moreover, FANCM was required for the recruitment of Bloom's syndrome proteins to DNA damage foci following collapse of the replication fork, which can be caused by ICL encounter, but not after ionizing radiation treatment.

To examine the effect of the interaction of FANCM with Fanconi anaemia core and Bloom's syndrome proteins in the DNA damage response, FANCM lacking MM1 and/or MM2 was ectopically expressed in FANCM-deficient cells. Loss of MM1 and/or MM2 increased cell sensitivity to mitomycin C, an ICL-inducing agent, indicating a requirement for both protein complexes in ICL repair. However, ubiquitylation of the Fanconi anaemia protein FANCD2 (mediated by the Fanconi anaemia core) and the formation of FANCD2 foci, which promote ICL repair, occurred independently of the presence of Bloom's syndrome proteins, as only loss of MM1 had an effect. Finally, both MM1 and MM2 were needed for the repair of sister chromatid exchanges (a phenotype of patients with Bloom's syndrome and a potential consequence of ICL). This suggests that the activation of this DNA damage response pathway requires the coordinated recruitment of both protein complexes to sites of ICL formation to prevent sister chromatid exchange.

This study reveals that FANCM bridges proteins of the Fanconi anaemia and Bloom's syndrome pathways and targets them to sites of DNA damage following replication fork collapse. Further research into this area might provide targets for the treatment of the two genetic disorders.

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ORIGINAL RESEARCH PAPER Dean, A. J. & West, S. C. FANCM connects the genome instability disorders Bloom's syndrome and Fanconi anemia. *Mol. Cell* **36**, 943–953 (2009)
FURTHER READING Huen, M. S. Y., Sy, S. M. H. & Chen, J. BRCA1 and its toolbox for the maintenance of genome integrity. *Nature Rev. Mol. Cell Biol.* **11**, 138–148 (2010)