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DNA REPLICATION

Partnering to unwind

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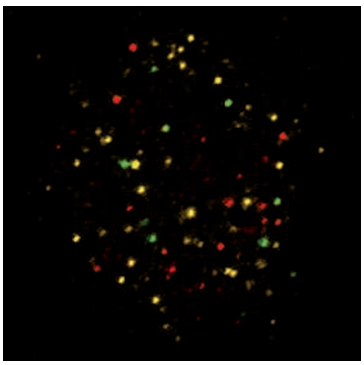
Accurate DNA replication is critical for maintaining genomic stability and preventing the accumulation of cancer-causing mutations that are characteristic of disorders such as Fanconi's anaemia (FA) and Bloom's syndrome (BS). Thirteen causative genes for FA have been identified, including the gene encoding the FA group J (FANCJ) helicase. Under replicative stress, FANCJ participates in the FA–breast cancer susceptibility (BRCA) pathway of DNA damage repair, but recent evidence suggests that it also functions independently of this pathway. In a study published in *The EMBO Journal*, Suhasini *et al*. have uncovered an interaction between FANCJ and BS helicase (BLM), and they show that these proteins cooperate functionally in the DNA damage response to replicative stress.



Foci containing Fanconi's anaemia group J (red) and Bloom's syndrome helicase (green) form in HeLa cells after exposure to the replication inhibitor hydroxyurea. Colocalization is shown in yellow. Image is reproduced, with permission, from Suhasini, A. N. *et al.* © (2011) Macmillan Publishers Ltd. All rights reserved.

FA cells are highly sensitive to agents that induce DNA interstrand crosslinks (ICLs), and the disease has been proposed to result from disruption of DNA repair. As both FANCJ and BLM respond to ICLs and replicative stress, the authors asked whether the two helicases interact. Indeed, FANCJ and BLM co-immunoprecipitated in HeLa cell nuclear extracts and in experiments using purified recombinant proteins. The interaction was direct and did not depend on DNA or proteins of the classic FA–BRCA pathway. Interestingly, the authors noted that in FA-J (a subtype of FA that is complemented by FANCJ) cells or HeLa cells depleted of FANCJ, BLM protein levels were decreased by 80–90%. BLM is degraded by a proteasome-mediated pathway when FANCJ is deficient.

Stress induced by hydroxyurea (HU) stalls replication; in these experiments, this resulted in the formation of foci where FANCJ and BLM partially colocalized. Similarly to BLM-depleted cells, FANCJ-deficient cells were sensitive to HU and exhibited a higher level of sister chromatid exchange than wild-type cells. HU sensitivity in FA-J cells was overcome by expression of wild-type FANCJ. Disruption of the endogenous FANCJ–BLM complex by expression of a FANCJ carboxy-terminal fragment that interacts with BLM resulted in cellular sensitivity to HU, suggesting a requirement for the physical interaction between the two DNA helicases.

So, do FANCJ and BLM work together in the repair process? The authors tested the ability of the proteins to unwind forked DNA substrates in strand displacement helicase assays and found that combining the two helicases resulted in a significant increase in the efficiency of unwinding damaged DNA. FANCJ worked synergistically with BLM (and not the related helicases, RecQ-like type 1 (RECQ1) or Werner's syndrome ATP-dependent helicase (WRN)) to unwind a DNA substrate with a sugar backbone discontinuity in the FANCJ-translocating strand.

Collectively, these studies have identified a new physical and functional association between the FANCJ and BLM helicases and contribute to our understanding of how DNA is unwound during damage repair. It will be interesting to see future mechanistic studies examining how the interaction between these proteins contributes to their ability to preserve chromosomal stability.

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ORIGINAL RESEARCH PAPER Suhasini, A. N. *et al.* Interaction between the helicases genetically linked to Fanconi anemia group J and Bloom's syndrome. *EMBO J.* 14 Jan 2011 (doi:10.1038/emboj.2010.362)