

FANCM: Motoring Forward in DNA Crosslink Repair?

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Fanconi anaemia (FA) is a cancer predisposition syndrome accompanied by bone marrow failure and congenital abnormalities. A distinguishing feature of FA patients and cells derived thereof is an exclusive hypersensitivity to DNA interstrand crosslinking (ICL) agents such as cis-platin. Recently, we have discovered that the vertebrate orthologue of archaeobacterial Hef is a bona fide FA protein, FANCM. The archaeobacterial Hef has interesting domain architecture with an N-terminal helicase domain and a C-terminal nuclease domain, which shares homology with XPF/Mus81 nucleases. Both domains have been implicated in the repair of stalled replication forks.

FANCM is part of the FA nuclear core complex and has biochemical activities similar to Hef. The exceptions are that this protein does not display a helicase activity but shows a weak translocase activity. FANCM has been proposed to link the FA pathway with DNA transactions required for ICL detection or repair. The discovery that the newly identified FAAP24 protein promotes a specific targeting of FANCM to DNA repair intermediates provides further evidence in this direction.

In order to determine whether the translocase or ATP hydrolysis activities of FANCM are required for FA pathway activation and subsequent ICL repair, we created a DT40 strain lacking the helicase domain. In addition, we also made a DT40 strain carrying a point mutation in the conserved Walker Box B motif of the helicase domain. Preliminary data show that both strains have almost wild type sensitivities to cis-platinum and mitomycin C, suggesting that the putative helicase/translocase function of FANCM is not required for FA pathway activation and cell survival in response to ICLs.

The point mutant, however, results in an increased level of spontaneous interchromatid crossovers, thus demonstrating an actual *in vivo* function for the putative helicase domain of FANCM. Interestingly this phenotype is shared with the yeast homologue of FANCM (MPH1), pointing to an evolutionarily conserved role for these proteins in suppressing crossover recombination. This is an important observation as normally cells actively suppress crossover recombination between sister chromatids (SCEs). This would prevent similar crossovers between homologous chromosomes that give rise to loss of heterozygosity that ultimately may lead to cancer.

Furthermore, our findings dissociate the enzymatic activity of the protein from its requirement for complex stability and ICL repair in the FA pathway. We hypothesise that the putative helicase function of FANCM is required to process the stalled/collapsed replication forks in a specific way so as to prevent crossover recombination.

Translational Applicability: A better understanding of FANCM's function in the repair of damaged DNA and FA pathway activation may have important implications for the development of treatment to correct the FA defect.