FANCM: fork pause, rewind and play

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DNA lesions or genomic regions that are difficult to traverse frequently hinder or block DNA replication. In response to replication fork stalling, the cell activates the replication stress response pathway, which acts to protect the fork from collapse, promotes the repair or bypass of the blockage and facilitates the resumption of DNA synthesis. In this issue of the EMBO Journal, two studies conducted by the Constantinou and Niedzwiedz laboratories shed light on how the DNA translocase FANCM acts to regulate the replication stress response (Luke-Glaser *et al*, 2009; Schwab *et al*, 2009). These studies help to explain how FANCM (mutated in the human cancer predisposition syndrome, Fanconi's anaemia (FA)) co-ordinately regulates checkpoint signalling and replication fork progression.

FA is a complex multigenic genomic instability disorder that can develop from a mutation in 1 of at least 13 different genes. Evidence suggests that the FA pathway acts in concert with nucleotide excision repair, translesion synthesis and homologous recombination to promote lesion repair/bypass, yet the mechanism by which this is achieved remains poorly understood. Cloning of the FANCM gene showed a putative DNA helicase/translocase that is related to Hef1, an *archaeobacteria* protein that maintains replication fork integrity (Meetei *et al*, 2005; Mosedale *et al*, 2005). Several studies have since established that FANCM is a potent DNA translocase that can remodel replication fork structures to promote fork regression (Gari *et al*, 2008). Surprisingly, it was shown that DNA translocase activity of FANCM is dispensable for its role in the FA pathway (Singh *et al*, 2009), but is instead essential for maintaining the integrity of stalled replication forks as part of the replication stress response (Collis *et al*, 2008).

Studies published by Luke-Glaser *et al* (2009) and Schwab *et al* (2009) in this issue of the EMBO Journal provide insight into the mechanism through which FANCM controls replication fork progression and contributes to replication stress response. Using DNA fibre analysis to directly visualize replication forks in mammalian cells, Luke-Glaser *et al* (2009) established that the DNA translocase activity of FANCM is required to restrain replication elongation; replication forks progress more quickly in the absence of FANCM and this leads to increased genomic instability. Similarly, Schwab *et al* (2009) found that replication forks are unstable in FANCM-deficient chicken DT40 cells and this leads to the accumulation of single-stranded DNA. Both groups also show

that the DNA translocase activity of FANCM is required for the efficient restart of stalled replication forks. Schwab *et al* found that an inability to restart stalled replication forks leads to inappropriate firing of nearby dormant origins, which is a hallmark of checkpoint deficiency.

FANCM was recently implicated in the ATR signalling pathway, which is central to the replication stress response (Collis *et al*, 2008). Studies by Luke-Glaser *et al* and Schwab *et al* corroborate this observation and provide further insight into the role of FANCM in this pathway. Both groups found that FANCM is important for eliciting efficient activation of the ATR checkpoint in response to various replication stress conditions: Schwab *et al* found that phosphorylation of Chk1 and Smc1 (ATR targets) is compromised in the absence of FANCM, and provide evidence that this defect is likely caused by a failure to efficiently recruit and/or retain TopBP1 on chromatin, which is essential for ATR activation (Kumagai *et al*, 2006). Luke-Glaser *et al* found that FANCM and Chk1 mutually stabilize each other. Thus, in the absence of FANCM, the ATR signalling pathway is not efficiently activated leading to replication fork instability (Figure 1; Collis *et al*, 2008; Luke-Glaser *et al*, 2009; Schwab *et al*, 2009).

How does FANCM facilitate ATR activation and promote replication fork restart? It is possible that remodelling of stalled replication forks by FANCM may facilitate interactions between TopBP1 and ATR, to promote its activation (Figure 1). FANCM may also act as a scaffold to coordinately recruit at least three key complexes to stalled replication forks; the ATR kinase complex (through direct binding to HCLK2), the FA core complex (through direct binding to FANCF) and Bloom's syndrome complex (through direct binding to RMI1 and TopoIII α ; Deans and West (2009)). Indeed, loss of FANCM confers phenotypes consistent with defects in all three complexes (Collis *et al*, 2008; Deans and West, 2009).

In summary, the current studies provide further insight into the role of FANCM in controlling replisome progression and fork dynamics in response to replication stress. The challenge over the next few years will be to determine how these critical functions of FANCM are regulated during cell cycle to ensure genome integrity.

Conflict of interest

The authors declare that they have no conflict of interest.

Figure 1 (A) Replication forks can be stalled by secondary structures or DNA lesions (star) that must be removed or by-passed for replication to proceed. The DNA translocase activity of FANCM remodels the stalled fork to facilitate activation of the ATR-ATRIP kinase complex. FANCM also interacts with HCLK2 and TopBP1 to further facilitate efficient ATR activation. FANCM may also act with the BLM helicase to facilitate replication restart. (B) Stalled forks are unstable in the absence of FANCM and accumulate extensive regions of ssDNA-RPA (red circles). Although the ATR-ATRIP complex is recruited to these sites, the checkpoint is not efficiently activated because of a failure to retain TopBP1 on chromatin and/or loss of Chk1.

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