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FANCJ at the FORK

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FANCJ, identified as a BRCA1-interacting partner

The story of *FANCJ* (*BACH1/BRIP1*) is similar to that of the first hereditary breast cancer genes, *BRCA1* and *BRCA2*. Initially characterized for function in DNA break repair and breast cancer suppression, their roles now extend to multiple activities in the DNA damage response and suppression of several cancers. FANCJ was the first BRCA1-interacting partner with known enzymatic activity and thus was considered a mediator of BRCA1 DNA repair function. It was thought that BRCA1 leveraged FANCJ helicase activity to unwind DNA in the vicinity of DNA damage. Consistent with this model, FANCJ was shown to function in double strand break repair in a manner dependent on BRCA1 binding [1]. Moreover, FANCJ clinical mutations were identified that disrupt its helicase activity and DNA repair function [2]. These findings, along with more comprehensive clinical analysis, suggested that breast cancer could arise from inherited mutations in *FANCJ* [3,4]. However, as the cast of BRCA-interacting partners has grown, the unfolding tale is that FANCJ is one of many factors functioning in BRCA-DNA repair and tumor suppression pathway.

FANCJ is a Fanconi anemia gene

Aside from breast and ovarian cancer [5,6], bi-allelic mutations in the hereditary breast cancer genes cause the rare genetic disorder Fanconi anemia (FA) that is responsible for birth anomalies, anemia, and cancer. Just two years after BRCA2 was found mutated in the FA-D1 complementation group [7], *FANCJ* was identified as the gene mutated in the FA-J complementation group [8–10]. Joining the FA circle, *BRCA1* was recently uncovered as the FA gene, *FANCS* [11]. This link between hereditary breast cancer and FA exemplifies the fact that the hereditary breast cancer proteins are multifunctional; important not only for DNA repair and tumor suppression, but also for normal proliferation and development (for a recent review see [12]). FA cells are very sensitive to agents that interfere with DNA replication, such as DNA interstrand crosslinks (ICLs). Thus, the link between BRCA proteins and FA also demonstrates that BRCA proteins function beyond DNA break repair to processing of stalled replication forks [13]. More recently, additional replication stress-associated functions have been uncovered. In particular, BRCA proteins protect stalled DNA

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replication forks from nuclease digestion [14,15]. Marching in step, FANCJ also functions at the replication fork, as outlined here, which likely contributes to genome stability and tumor suppression.

FANCJ interfaces with replication

In support of replication fork-associated functions, FANCJ is present at forks in a replication-dependent manner. Localization studies reveal that FANCJ tracks with BRCA1 not only in nuclear foci and at DNA lesions, but also to sites coincident with proliferating cell nuclear antigen (PCNA) and at DNA replication forks [1,16–21]. Similar to BRCA1, FANCJ localization to DNA crosslinks or chromatin following crosslink induction is dependent on replication [22,23]. An interface with replication is also suggested by proteomic analysis of proteins associated with nascent DNA. FANCJ is found directly at active-, stalled-, and collapsed replication forks [20,21]. One could speculate that the BRCA1-FANCJ interaction is uniquely required for some aspect of the replication stress response. Indeed, FANCJ and BRCA1 interact most robustly during S phase [24]. Moreover, not all BRCA-associated partners localize to replication forks or chromatin in a replication dependent manner. For example, BRCA1-associated CtIP weakly accumulates in chromatin following an ICL in a replication independent manner [23].

FANCJ shares functions with BRCA1 in the replication stress response

Although the localization of FANCJ to replication forks does not foretell its function, the consequence of FANCJ deficiency provides clues that, similar to BRCA1, FANCJ has function outside of break repair. While data vary from cell system analyzed, FANCJ deficient cells typically have a broad sensitivity to replication inhibitors, such as ICL-inducing agents, mitomycin C (MMC), melphalan and cisplatin as well as to hydroxyurea (HU), which depletes deoxyribonucleotide pool, and to aphidicolin, which inhibits DNA polymerases. In contrast, FANCJ deficient cells have minor sensitivity to agents that induce DNA double strand breaks (DSBs), such as ionizing radiation (IR) and camptothecin. The mild sensitivity to DSB-inducing agents and lack of sensitivity to ultraviolet light (UV) irradiation distinguishes FANCJ deficient cells from BRCA-deficient cells [8,18,25–27] (see Supplemental Table 1). Nevertheless, IR-induced DNA double strand breaks and UV-induced DNA intrastrand crosslinks are repaired with reduced kinetics in BRCA1- or FANCJ-deficient cells [17,18,28]. Moreover, RPA-coating of ssDNA in S phase cells following UV irradiation and subsequent checkpoint responses are defective in these cells. Likewise UV induced mutations are enhanced by deficiency in either FANCJ or BRCA1 [18,28]. In the response to IR, evidence also suggests that similar to BRCA1, FANCJ promotes checkpoint activation and maintenance [16,29,30]. Failure to elicit proper checkpoint responses could underlie the defective replication restart in FANCJ or BRCA1 deficient cells after release from aphidicolin treatment [31–33]. Functions in the replication stress response could protect the genome beyond S phase given that both BRCA1 and FANCJ impacts centromere amplification following replication stress [34,35].

While FANCJ deficient cells resemble BRCA1 deficient cells in several respects, it remains to be determined what key functions are shared. This understanding could clarify why unlike

BRCA1 deficient mice, FANCJ deficient mice are viable [36–40]. In particular, it will be important to address if FANCJ functions with BRCA1 in protecting stalled forks from nuclease digestion, loading of the 9-1-1 complex, checkpoint activation, recruitment of repair factors such as FANCD2 or evicting the CMG (Cdc45, MCM2-7, and GINS) replicative DNA helicase from chromatin in ICL repair [41–43]. In support of the possibility that FANCJ helicase or translocase activities could support one or more of these fork-processing activities, in FANCJ deficient cells Cdc45 remains aberrantly loaded on chromatin after IR [16], and FANCD2 foci are reduced [44,45].

FANCJ resolves secondary structures at stalled forks

It also remains unexplored as to if BRCA1 functions with FANCJ in its metabolism of replication-associated structures. In particular, FANCJ counteracts fork stalling and genomic instability by resolving secondary structures such as G-quadruplexes (G4s) that form in guanine-rich DNA [13,40,46–49]. In accordance, loss of FANCJ in Xenopus egg extract system leads to persistent replication stalling at G4s [50]. Likewise, cells deficient in FANCJ are sensitive to G4 binding drugs [47,51]. Suggesting that G4s are abnormally accumulating even in the absence of exogenous replication stress, FANCJ deficient chicken cells have a delay in S phase progression that correlates with decreases in replication fork velocity and ssDNA induction [51]. Moreover, unchallenged FANCJ null mouse or deficient human cells show slower replication fork extension rates and slower progression through S phase consistent with increased replication fork stalling [40,52]. Whereas FANCJ deficient cells have an elevated S-phase accumulation in response to low dose aphidicolin, FANCJ null cells show signs of DNA break induction with high dose aphidicolin suggesting replication fork collapse [16,33]. The nature of the genomic instability may be species specific given that FANCJ deficiency confers loss of G4s in *C. elegans*, telomere abnormalities in human cells, and microsatellite instability (MSI) in mouse and human cells [40,46,53–56]. Resolving secondary structures could maintain chromatin structure given that FANCJ deficient DT40 cells have increased heterochromatin formation, localized changes in histone modifications, and gene expression [49,51]. It remains to be determined how replication fork preservation functions relate to one or more of FANCJ described in vitro enzyme functions. FANCJ is an ATPase/helicase/translocase that unwinds DNA in a 5′-3′ direction and is active on a range of substrates such as 5′ flaps, forked DNA duplexes, D loops, and G4s and can displace protein/DNA interactions [2,46,47,57,58].

Loss of FANCJ-BRCA1 interaction alters the replication stress response

Despite restart defects in BRCA1 deficient cells, it is unlikely that BRCA1 binding to FANCJ is required for FANCJ function in resolving replication-blocking structures given that resistance to replication stress is enhanced in cells lacking the FANCJ-BRCA1 interaction [31,33,59]. Notably, expression of a BRCA1-interaction defective mutant, $FANCJ^{S990A}$ in FANCJ-null FA patient cells confers greater resistance to cisplatin, MMC, melphalan and UV as compared to expression of wild-type FANCJ [60]. Likewise in chicken cells the FANCJ-BRCA1 interaction is not required for ICL resistance, nor appear to be conserved [25]. Thus, one could speculate that in human cells, the FANCJ-BRCA1 interaction has a distinct replication stress associated function. Consistent with this idea, cells deficient

in the FANCJ-BRCA1 interaction have defects in checkpoint and repair responses [59]. Resembling BRCA1- or FANCJ-deficient cells, FANCJ^{S990A} cells fail to arrest DNA synthesis following IR and show reduced double strand break repair by homologous recombination (HR) [16,60]. Not only are cells expressing FANCJ^{S990A} more sensitive to agents that induce DSBs, HR is reduced to the level found in cells expressing the helicase inactive mutant, FANCJ^{K52R} [60]. Resistance to replication-stress inducing agents such as MMC and UV is managed through enhanced DNA damage tolerance pathways including increased reliance on the translesion synthesis (TLS) polymerase, polη [60]. Thus, in human cells, the FANCJ-BRCA1 interaction could serve to coordinate the HR and TLS pathways to facilitate repair and recovery of replication with minimal error induction. While the interaction may not be required to restart replication, it will be worth considering if the FANCJ-BRCA1 interaction preserves fragile sites under replication stress given that BRCA1 and FANCJ share this function [40,61,62].

Cells lacking the FANCJ-BRCA1 interaction could have an altered replication stress response because FANCJ is not functional. With respect to replication forks, data suggest FANCJ localization is not dependent on BRCA1. In particular FANCJ localizes to UV lesions in S phase before BRCA1 and independent of BRCA1 binding. Thus, in contrast to DNA breaks, FANCJ localization to stalled forks appears to be independent of BRCA1[16,18]. Alternatively, FANCJ could fail to be properly modified. In support of this idea, FA-J cells expressing the BRCA1-interaction defective mutant, FANCJ^{S990A} resemble FA-J cells expressing an acetylation-defective mutant, FANCJ^{K1249R}. In these cells, ICL resistance is conferred with reduced dependence on HR factors and enhanced reliance on TLS factors [63]. Acetylation at FANCJ lysine K1249 promotes DNA end resection and checkpoint maintenance [63]. Thus, these functions could also be promoted by BRCA1 binding. Another possibility is that when unbound to BRCA1, FANCJ fails to interact with other partners. For instance, loss of FANCJ binding to BLM or RPA could derail FANCJ's end processing or checkpoint functions [27,64]. As compared to wild-type FANCJ, FANCJ^{S990A} precipitates less of the replication checkpoint factor, TopBP1 following IR suggesting that BRCA1 binding impacts the interactions of FANCJ with other partners. The defective binding does not result from loss of a critical TopBP1 binding domain. Threonine 1133 of FANCJ is phosphorylated following DNA damage and this mediates its direct interaction with the C-terminal BRCT repeats of TopBP1. Given that FANCJ binding promotes TopBP1 stabilization at stalled forks, ATR activation and the intra-S phase checkpoint activation [65], a reduction in this interaction could switch repair processing. Likewise, loss of BRCA1 or TopBP1 binding and reduced checkpoint responses could underlie the aberrant induction of new replication in FANCJ deficient cells [44]. Loss of BRCA1 binding to FANCJ could also unleash FANCJ or its helicase activity to create a gain-of-function. For example, the enhanced TLS associated with BRCA1 deficiency in response to UV could stem from an increase in unregulated FANCJ, mimicking the enhanced TLS found in cells expressing FANCJ^{S990A} [28,60]. In addition, it will be important to consider if altered FANCJ function is a contributing factor to replication fork protection defects that are found in BRCA1 deficient cells or when BRCA1 is in the heterozygous state [66]. If so, unregulated FANCJ could also contribute to replication-stress associated defects in breast cancers in which FANCJ is overexpressed [67].

The FANCJ-MLH1 interaction is essential for replication restart

In contrast to the finding that FANCJ binding to BRCA1 is indispensable for cells to recover from replication stress, FANCJ binding directly to the mismatch repair (MMR) protein, MLH1 is essential. Not only does expression of an MLH1-interaction defective mutant, $FANCJ^{K141/142A}$, in FANCJ-null patient FA-J cells fail to restore ICL resistance, but also as compared to FANCJ-null cells, ICL sensitivity is enhanced. Moreover, expression of $FANCJ^{K141/142A}$ exacerbates the abnormal ICL-induced G2/M accumulation in FANCJ-null cells [26]. Correspondingly, a hereditary colon cancer mutation $MLH1^{L607H}$, which is defective in FANCJ binding, confers increased ICL sensitivity and checkpoint defects not previously detected in MLH1-null cells [68]. Thus, mutations in FANCJ or MLH1 that disrupt the FANCJ-MLH1 interaction sensitize cells to ICLs to a greater extent than deficiency in FANCJ or MLH1 [26,68,69]. A heightened replication stress response is also detected upon release from aphidicolin. Cells lacking the FANCJ-MLH1 interaction remain arrested while FANCJ-null cells re-enter the cell cycle. The arrest correlates with γ-H2AX and DNAPKcs phosphorylation, suggesting fork breakage. Collectively, these data indicate that deficiency in the FANCJ-MLH1 interaction is worse for the restart of replication than deficiency in FANCJ or MLH1 alone.

MSH2 depletion suppresses replication restart defects in cells lacking the FANCJ–MLH1 interaction

While the underlying cause of the replication restart defect and fork collapse in cells lacking the FANCJ-MLH1 interaction is not known, it is linked to the mismatch repair protein, MSH2. Specifically, depletion of MSH2 suppresses not only MMC-induced sensitivity and chromosomal aberrations, but also aphidicolin-induced replication restart defects and break induction in cells lacking the FANCJ-MLH1 interaction [33]. This finding supports a model in which FANCJ, through its MLH1 interaction, unwinds DNA structures or displaces MSH2 from DNA structures to restart stalled replication forks. MMR proteins accumulate at replication forks [20] and are poised to bind DNA mismatches or secondary structures. Therefore, if not regulated, the MMR pathway could activate checkpoints, repair, and apoptotic responses that counteract the restart of stalled replication forks. There is precedent for the regulation of DNA repair pathways by helicases, such as yeast Srs2 and bacterial UvrD (helicase II) [70,71] and FANCJ's closest human homologue, RTEL [72]. Alternatively, FANCJ could promote MMR function at stalled forks in repair or checkpoint responses. In support of this point, MMR is required for FANCJ localization to ICLs [19] and UV light-induced DNA crosslinks [18]. Moreover, an interaction between FANCJ and MSH5 is important for repair of camptothecin-induced breaks [73]. Furthermore, a robust checkpoint response to DNA alkylation or UV damage requires FANCJ, and the FANCJ-MLH1 interaction [18,68]. Collectively, these findings suggest that FANCJ regulates the MMR response to replication stress; without FANCJ, MMR complexes could be detrimental as they block replication fork progression or fail to mount a productive response. In future studies, it will be important to understand if an ineffective MMR complex explains why similar to MMR deficiency, FANCJ deficiency confers microsatellite instability (MSI) and lymphoma [40].

In summary, FANCJ has not receded from center stage. Rather, FANCJ is part of a BRCA network whose function in the replication stress response is an evolving story that likely involves replication stress induced arrest and restart functions (Figure 1). Building a more complete picture will be fundamental to grasp not only a full understanding of its function in DNA repair and tumor suppression pathways, but also to recognize opportunities for future therapy intervention.

Supplementary Material

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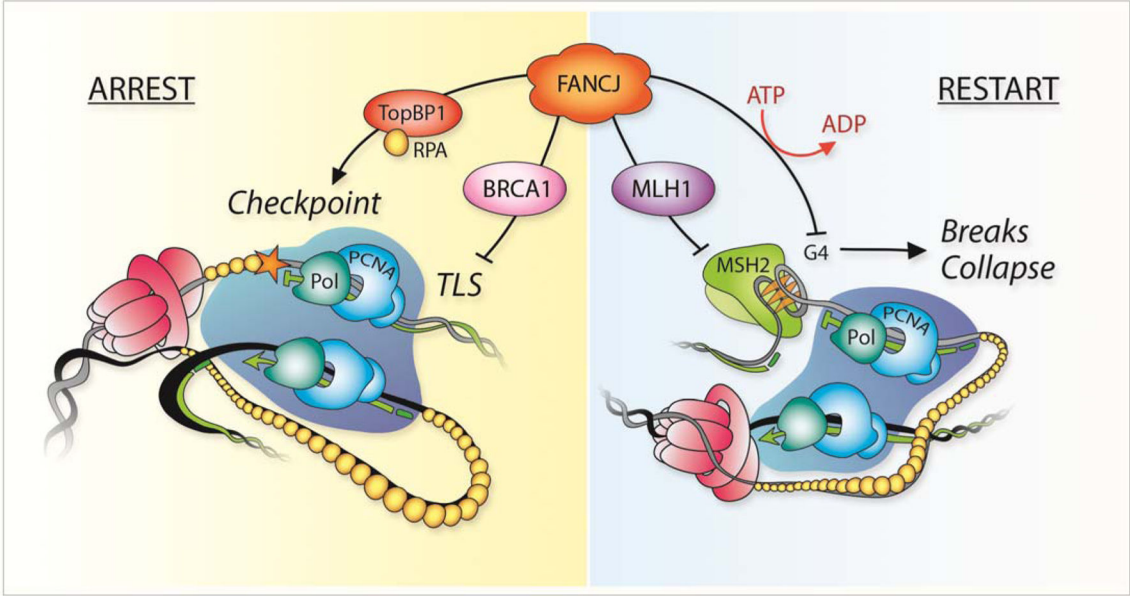

Figure 1.

Potential role for FANCJ in the replication stress response: In response to replication arrest, FANCJ interactions with ToBP1 and BRCA1 promote checkpoint activation and inhibit translesion synthesis (TLS). Following repair processing, FANCJ interaction with MLH1 and helicase/translocase activities promote replication restart through displacement of MSH2 complexes and unwinding of secondary structures, such as G4s as shown.