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Assembling an orchestra: Fanconi anemia pathway of DNA repair

Fenghua Yuan[1], Limin Song[1], Liangyue Qian[1], Jennifer J. Hu[1,2], Yanbin Zhang[1]

[1]Department of Biochemistry and Molecular Biology, [2]Department of Epidemiology and Public Health, University of Miami Miller School of Medicine, Miami, FL 33136, USA

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1. ABSTRACT

Fanconi anemia (FA) is a recessive genetic disorder characterized by developmental defects, bone marrow failure, and cancer susceptibility. The complete set of FA genes has only been identified recently and seems to be uniquely conserved among vertebrates. Fanconi anemia proteins have been implicated in the repair of interstrand DNA crosslinks that block DNA replication and transcription. Although all thirteen FA complementation groups show similar clinical and cellular phenotypes, approximately 85% of patients presented defective FANCA, FANCC, or FANCG. The established DNA interacting components (FANCM, FANCI, FANCD2, and FANCJ) account only for ~5% of all FA patients, an observation that raises doubt concerning the roles of FA proteins in DNA repair. In recent years, rapid progress in the area of FA research has provided great insights into the critical roles of FA proteins in DNA repair. However, many FA proteins do not have identifiable domains to indicate how they contribute to biological processes, particularly DNA repair. Therefore, future biochemical studies are warranted to understand the biological functions of FA proteins and their implications in human diseases.

2. INTRODUCTION

Fanconi anemia (FA) is a severe chromosomal instability disorder characterized by developmental defects, aplastic anemia, chromosomal instability, and predisposition to leukemia and solid tumors (1-12). Another hallmark of FA, which is also a reliable cellular marker for clinical diagnosis, is its hypersensitivity to the synthetic DNA interstrand crosslinking compounds including mitomycin C (MMC), cisplatin, and diepoxybutane (DEB) (8, 13). Upon treatment with these DNA crosslinkers, FA cells display dramatically increased genomic aberrations, including chromosome breaks and radial chromosomes (8, 12), indicating that Fanconi anemia proteins are involved in repairing DNA interstrand crosslinks (ICLs). ICL covalently tethers both strands of the double helix and blocks essential DNA transactions including replication and transcription. It seems that DNA replication is the most important factor to elicit repair and also toxicity of ICLs (14-16). FA proteins are believed to function in stabilizing replication forks and assisting the replication machinery to deal with ICLs and other DNA lesions or structures that hinder the progression of replication forks (17-24).

It has also been well documented that FA proteins are directly involved in mitigating oxidative stress (25-32), and FA deficient cells display hypersensitivity to elevated oxidants (33-40). Increased susceptibility to oxidants is believed to contribute to the bone marrow failure associated with FA (32). Coincidently, oxidative stress is the most prominent endogenous source of ICLs, via generation of the lipid peroxidation products malondialdehyde, 4-hydroxynonenal, acrolein, and crotonaldehyde (35, 41-44).

Thirteen Fanconi anemia genes have been identified thus far (*FANC-A, -B, -C, -D1/BRCA2, -D2, -E, -F, -G, -I, -J/BRIP1/BACH1, -L, -M,* and *-N/PALB2*) (45-63). FA proteins were classified into three groups according to their roles in the monoubiquitination of FANCD2 and FANCI, a critical step in the ICL repair (5). Group I is composed of eight FA proteins, FANC-A, -B, -C, -E, -F, -G, -L, and -M. These proteins are components of the FA core complex. A major function of the core complex is to activate the group II proteins, FANCD2 and FANCI complex (ID complex), by monoubiquitination particularly when cells are under genotoxic stress (53, 54, 60, 64-66). Cells that are defective in any of group I proteins are deficient in monoubiquitination of the ID complex. It is worth mentioning that the activation of FANCD2 and FANCI also occurs spontaneously (likely in response to naturally occurring replication-stalling damage), or can be induced by DNA damaging agents or stresses other than DNA crosslinkers, such as ionizing radiation, ultraviolet radiation, aphidicolin, or hydroxyurea (20, 64, 67-69). Downstream of or parallel to the monoubiquitination of the ID complex are the group III proteins, FANCD1/BRCA2, FANCJ/BRIP1, and FANCN/PALB2. These proteins are involved in the repair of double strand breaks produced during the 'unhooking' of ICLs (5, 7, 70), and constitute a FA-BRCA network to guard genomic integrity (5, 64). A collection of excellent reviews provides great insights into the mechanism how FA proteins are involved in the DNA damage response and repair (4, 5, 7, 9, 10, 12, 19, 43, 70-73). The focus of this review is to summarize some of the recent progress on FA protein studies and to provide our perspective on how FA proteins participate in the repair of ICLs.

ICL repair is highly complex and unique among all repair pathways, because multiple players from established DNA repair pathways have to work coordinately in order to remove a single interstrand crosslink lesion. In addition to FA proteins, other proteins involved in nucleotide excision repair (NER), translesion synthesis (TLS), mismatch repair (MMR), and homologous recombination (HR) also participate in ICL repair (5, 7, 16, 43, 74-83). In this review, we discuss the potential mechanisms how FA proteins collaborate with multiple DNA repair pathways and exert their functions in maintaining the stability of replication forks.

3. FANCONI ANEMIA CORE COMPLEX – COMPOSER, CONDUCTOR, AND MUSICIAN?

Extensive interaction studies have shown that eight of the FA proteins form a multi-subunit nuclear core complex: FANCA, FANCB, FANCC, FANCE, FANCF, FANCG, FANCL, and FANCM (5, 12). The FA core complex was successfully purified from HeLa cells through immunoprecipitation with a FANCA-specific antibody (65, 84). This protein-association technique was successfully used by Weidong Wang's group to identify three FA genes, *FANCB*, *FANCL*, and *FANCM* (46, 60, 65, 85). Two additional FANCA-associated proteins, namely FAAP24 and FAAP100, have also been identified to be components of the core complex although no FA patients with mutations in these genes have been identified thus far (86, 87). The 10 proteins in the FA core complex may exist in the form of subcomplexes, i.e. FANCM-FAAP24, FANCA-FANCG, FANCB-FANCL-FAAP100, and FANCC-FANCE-FANCF (5, 86, 88-91). HES1, a transcriptional repressor, is also reported to be associated with the FA core complex (92, 93). In addition to its critical function of monoubiquitinating the ID complex, FA core complex is also known to be directly involved in a wide spectrum of other functions as described below.

3.1. Components of the FA core complex are phosphorylated under genotoxic stress

The presence of any DNA damage that is bulky enough to impede the progression of replication forks is likely to be initially detected by the replication machinery. Upon stalling of the replicative DNA polymerase, the MCM (minichromosome maintenance) helicase in the replication machinery continues to unwind DNA ahead of the fork, resulting in exposure of single-stranded DNA (94). The single-stranded DNA is quickly coated by ssDNA binding protein RPA to prevent degradation by DNA nucleases. More importantly, this RPA-coated ssDNA serves as an anchor to independently recruit ATR-ATRIP, Rad17-RFC, the 9-1-1 complex, and claspin, leading to the activation of the ATR DNA damage response pathway, and resulting in an intra-S checkpoint (94-96). Since ICLs present an essentially unsurmountable barrier for DNA helicases, one might expect the checkpoint activation by ICLs to be limited due to lack of ssDNA exposure. However, ICL damage actually does activate the ATR damage response pathway, resulting in an S-phase checkpoint arrest (97). Intriguingly, this checkpoint activation requires the FA core complex and FANCD2 (97-100). Thus FA proteins appear to act as replication-coupled DNA damage sensors in this scenario (18, 20).

It is known that the activated ATR-CHK1 kinases phosphorylate many FA proteins, with implications for DNA repair (Figure 1). Phosphorylation of FANCA on serine 1449 by ATR kinase in response to DNA damage is known to be essential for the FA pathway (101). Although the $FANCA^{S1449A}$ mutant localizes normally to chromatin, it fails to correct a variety of FA-associated phenotypes including the FANCD2 monoubiquitination deficiency (101). FANCE is phosphorylated at theronine 346 and serine 374 by CHK1. The non-phosphorylated mutant of $FANCE^{T346A/S374A}$ allows normal level of FANCD2 monoubiquitination and FANCD2 foci assembly, but fails to complement the hypersensitivity of FANCE-deficient cells to the synthetic crosslinking agent, mitomycin C (102). The phosphorylation of FANCE by CHK1 leads to

its degradation and has been suggested to be a negative regulation mechanism of FA pathway (12). The putative phosphorylation of FANCM by ATR kinase increases its binding affinity for chromatin (60, 103, 104). Furthermore, hyperphosphorylation of FANCM by Plk1 kinase (polo-like kinase) is involved in the cell cycle dependent recruitment of the core complex to chromatin (103, 105). This phosphorylation provides an important layer of regulation that ensures the FA core complex is recruited to chromatin only during S phase, but not mitosis phase of the cell cycle.

In summary, the phosphorylation of the FA core complex is likely to affect stability of the core complex, ubiquitin ligase activity, chromatin association, and repair functions. It is worth noting that the WD40 repeats of FANCL may be involved in binding to the phosphorylated serine or threonine (106), therefore serving as a platform to bring together the phosphorylated subcomplexes FANCA-FANCG (phospho-FANCA), FANCE-FANCC-FANCF (phospho-FANCE), and FANCM-FAAP24 (phospho-FANCM) with FANCL-FANCB-FAAP100 in order to form the FA core complex in response to DNA damage. In line with this, the WD40 repeats of FANCL are reported to be required for assembly of the FA core complex (107).

3.2. FA core complex is a multi-subunit E3 ubiquitin ligase

A hallmark and convenient diagnostic marker of FA is the monoubiquitination of FANCD2 (108, 109). All 10 known subunits of the FA core complex are indispensable for the FANCD2 monoubiquitination (46, 64, 65, 86, 87). Very recently, FANCI, an interacting partner of FANCD2, was also found to be monoubiquitinated by the FA core complex (53, 54). It is now clear that FANCD2 monoubiquitination occurs via FANCL-mediated E3 ubiquitin ligase activity (65). FANCL modifies FANCD2 at lysine 561 by adding a single ubiquitin molecule with UBE2T acting as the E2 ubiquitin-conjugating enzyme (110). It is currently unknown how other components of the FA core complex facilitate or regulate the FANCL ubiquitin ligase in response to DNA damage. However, assembly of the FA core complex per se does not seem to trigger the FANCD2 monoubiquitination. Instead, the damage-induced recruitment of the FA core complex and the independent recruitment of UBE2T to chromatin play a critical role in regulating the FANCD2 monoubiquitination (111).

3.3. Is FANCM-FAAP24 the only core component that recognizes DNA?

Thus far, FANCM-FAAP24 is the only known DNA-binding component in the FA core complex (60, 86). FANCM contains a DEAH-box helicase domain and an endonuclease domain (60). In human FANCM, the endonuclease domain is thought to be degenerate since its ERCC4 endonuclease catalytic motif ERKxxxD has diverged to ERRxxxE (60, 75). To date, no DNA helicase or endonuclease activity has been detected in FANCM. Nevertheless, FANCM can remodel stalled replication forks through fork reversal and branch migration, thus stabilizing the stalled replication forks and providing temporal and spatial access for the damage to be repaired (22, 23). The ATP-dependent branch-point migration activity of FANCM does not seem to be required for the monoubiquitination of FANCD2 and FANCI, but is needed for its role in the ATR/Chk1 damage signaling and the repair of crosslinks through recombination (24, 100, 112). Using *Xenopus* egg extracts, Sobeck *et al* showed that the chromatin recruitment and the damage-induced phosphorylation of FANCM are mediated by both FANCD2 and the ATR/ATM pathways, indicating that FANCM may also act downstream of FANCD2 and have multiple roles in chromosomal replication (104).

FANCM appears to be responsible for recruitment of the FA core complex to chromatin (60, 75, 86-89, 103). The monoubiquitinated ID complex may also be recruited to chromatin through a FANCM-dependent mechanism (53, 61, 64, 113). However, unlike other factors in the core complex, FANCM is not required for the formation of the eight-subunit (but not the 10-subunit) core complex (103) and $FANCM^{-/-}$ cells are partially deficient in damage-induced FANCD2 monoubiquitination (112, 114). $FANCM^{-/-}$ knockout mice further support that FANCM may have a stimulatory but not essential role in monoubiquitinating FANCD2 (115). These observations suggest that FANCM may not be the only DNA binding component in the FA core complex and that the FA core complex may also be recruited to DNA through components other than FANCM.

Additionally, a direct interacting partner for FANCM-FAAP24 in the FA core complex has not been identified thus far, although FANCM-FAAP24 was originally identified through protein association in a FANCA-specific immunoprecipitation assay (19, 60, 84). $FANCM^{-/-}$ cells are sensitive to camptothecin, a topoisomerase inhibitor. Susceptibility to camptothecin is a unique feature identified only for FANCD1/BRCA2 and FANCN/PALB2, but not for components of the FA core complex (114). These data indicate that FANCM may function in both FA core complex dependent and independent pathways (114, 115), and that the FA core complex may alternatively be recruited to chromatin or damaged replication forks through other mechanisms, e.g., additional unknown DNA binding or damage recognition factors present in the FA core complex.

Very recently, the sole identified FANCM patient, EUFA867, was reported to have additional defects in the *FANCA* gene (biallelic mutations) (114), which raises concerns as to whether *FANCM* is an actual FA gene (8). Additionally, patient EUFA867 exhibited a much milder and therefore atypical clinical phenotype relative to other FA patients (114), supporting the notion that the FANCA deficiency may be attenuating the severity of FANCM deficiency. This phenomenon is also observed when FANCM was disrupted in a FANCC-deficient background (61). These data suggest that, in the absence of FANCM, the alternative processing of ICLs by FA core components is likely to produce more deleterious effect compared to processing that involves FANCM participation.

3.4. Functions of FANCA, FANCB, FANCC, FANCE, FANCF, FANCG, and FAAP100

This group of identified FA factors comprises newly evolved proteins in vertebrates and currently lacks identifiable domains and motifs to suggest what biological activities they may have (70). Intriguingly, mutations in FANCA, FANCC, and FANCG make up 85% of the FA patient population (8, 12). The best characterized functions of these proteins are to facilitate the monoubiquitination of FANCD2 by FANCL as described above, to directly mitigate oxidative stress, and/or to enable cells to repair DNA damage.

3.4.1. Functions in DNA repair

Although direct evidence in DNA transaction is lacking, this group of FA proteins play critical roles in DNA damage response and repair. The similar cellular phenotypes, including sensitivity to DNA damaging agents, increased spontaneous and damage-induced chromosomal aberrations, and reduced damage-induced base substitution mutagenesis, unequivocally establish the DNA repair functions of these FA proteins. These FA core components seem to be involved in all major steps of the ICL repair including ICL unhooking, bypass, and fork reestablishment through homologous recombination. The FA core complex may play more important roles in interacting with and repair of DNA damage than currently appreciated.

FANCA, FANCC, and FANCG knockout mice show similar phenotype in terms of sensitivity to DNA crosslinking agents and chromosomal instability (116-121). FANCA and FANCG were shown to be required for the DNA double strand break-induced ICL repair in human cells (78). Using nuclear protein extracts and complementation analysis, it was demonstrated that FANCA, B, C, F, and G are all required for efficient incisions at the sites of psoralen-mediated ICLs (122, 123). FANCA was also found to be involved in the psoralen ICL-induced mutagenesis in lymphoblasts, implicating its involvement in the mutagenic TLS of DNA damage (124). Furthermore, both FANCA and FANCG are necessary for efficient spontaneous and UV-induced base substitution mutagenesis in human fibroblasts (82). FANCA is required for recruiting RAD51 and BRCA2/FANCD1 into the MMC-induced nuclear foci, indicating its role in the homologous recombination repair of ICLs (125). In avian DT40 cells, FANCC was shown to function together with BRCA2/FANCD1 and RAD51 to repair double strand breaks (DSB) produced during replication in an epistatic manner (126). FANCG is associated with FANCD1/BRCA2 and XRCC3 (RAD51 paralog) during homologous recombination by direct interactions (127, 128). In FANCG-knockout CHO cells, defects in homologous recombination and non-homologous end joining were also observed (17). These data suggest direct involvement of the components of the FA core complex in DNA repair. Biochemical characterization of these FA core proteins and their interactions with DNA should greatly help us understand how they are involved in DNA metabolism.

3.4.2. Functions in mitigating oxidative stress

There is a large body of evidence supporting that FA cells are hypersensitive to oxidative stress and FA proteins are involved in mitigating the effect of such stress (25-36). Cytochrome P450 2E1 (CYP2E1), a drug metabolism enzyme involved in the production of ROS intermediates and frequently localized to nuclei (129), was shown to interact with and be down-regulated by FANCG (29). Through direct interaction, FANCG also increases the activity of mitochondrial peroxidase peroxiredoxin-3 (PRDX3), a mitochondrial antioxidant enzyme (130). Additionally, FANCA and FANCG are redox-sensitive proteins. In response to the oxidative stress, both FANCA and FANCG are multimerized through intermolecular disulfide linkage (31). FANCA forms a stable complex with FANCG and may help the nuclear localization of FANCG (88). Since both FANCG and FANCC can be localized to nucleus through interaction with the nuclear localization signal-containing FANCA and FANCE respectively (70, 91), we speculate that FANCG and FANCC may be involved in suppressing the oxidative stress in the nucleus. This putative function will be helpful to prevent the formation of oxidative DNA damage and link the oxidative stress hypothesis and the DNA repair hypothesis to the etiology of Fanconi anemia.

Furthermore, FANCC has been shown to interact with NADPH cytochrome P450 reductase and suppress its activity in triggering the production of reactive oxygen species (ROS) (30). FANCC also interacts with glutathione S-transferase P1-1 and significantly increases its antioxidant activity (131). Comparing with cells from other FA subtypes, FANCE-deficient cells show the highest degree of DNA oxidation after H_2O_2 treatment, indicating that FANCE may also be involved in the modulation of oxidative stress response (132).

4. ID COMPLEX – CONDUCTOR

FANCI is the most recently identified FA gene and the last assigned FA complementation group (53-55). It is a paralog of FANCD2 and its C-terminus interacts with FANCD2 to form a complex called the ID complex (21, 53). It has been noted that FANCI and FANCD2 are not always found together in the ID complex. In a reconstitution analysis in insect cells, only ~5% of FANCI was found to form a complex with FANCD2 (21). Both FANCI and FANCD2 are leucine rich proteins (21) and both proteins are monoubiquitinated by the FA core complex under genotoxic stress (53, 59, 64). This modification is considered to be essential for the FA pathway to exert its effects, especially in reestablishing replication forks through homologous recombination.

4.1. ID complex is phosphorylated, monoubiquitinated, and deubiquitinated under genotoxic stress

Under genotoxic stress, both FANCI and FANCD2 can act as substrates of ATR/ATM (ataxia telangiectasia and Rad3-related/ataxia telangiectasia-mutated) kinases (53, 67, 133). The phosphorylation of FANCI may function as a molecular switch to turn on the FA pathway (134). The phosphorylation of FANCD2 is required for DNA damage-induced intra-S phase checkpoint and for cellular resistance to DNA crosslinking agents (133, 135). However, another study suggests that

FANCD2 phosphorylation is dispensable for resistance to cisplatin and for FANCD2 monoubiquitination (134).

The monoubiquitination of FANCD2 plays a critical role in cellular resistance to DNA crosslinking agents and is required for FANCD2 to form damage-induced nuclear foci with BRCA1, FANCD1/BRCA2, RAD51, FANCJ/BRIP1, FANCN/PALB2, and gamma-H2AX on chromatin during S phase of the cell cycle (62, 64, 66, 136-141). Under genotoxic stress, FANCD2 is monoubiquitinated at lysine 561 and FANCI is monoubiquitinated at lysine 523 by the FA core complex (53, 59, 64, 142, 143). While there is no disagreement on the importance of the FANCD2 monoubiquitination, the importance of the FANCI monoubiquitination is in dispute (53, 134). The monoubiquitination of FANCI seems to rely on the FANCD2 monoubiquitination (53, 70). Nevertheless, the presence of FANCI increases monoubiquitination and also restricts it to the physiological lysine site on FANCD2 in an *in vitro* reconstituted system (142), although this ubiquitination site on FANCD2 does not seem to be critical based on the fact that FANCD2 K561R-ubiquitin fusion protein complements the defects of the *FANCD2* knockout DT40 cells (144).

The deubiquitination of FANCD2 by USP1-UAF1 is an important mechanism to keep the FA pathway in check under unstressed conditions. Down regulation of USP1 by transcriptional repression and DNA damage-dependent autocleavage shifts the ubiquitination balance toward increased monoubiquitination of FANCD2 and FANCI and therefore triggers downstream repair events (12, 101, 145-148). However, in chicken DT40 cells, the monoubiquitination of FANCD2 has been shown to be independent of USP1 autocleavage and the deubiquitination of FANCD2 is required for DNA crosslink repair (149).

4.2. ID complex recognizes branched structures

Purified human FANCD2 has been reported to bind double-stranded DNA and Holliday junctions (150). However, in a very recent study, the unmodified FANCD2 was found to have higher affinity to single-stranded DNA over Holliday junction and dsDNA (151). Research from both Patrick Sung's group as well as our laboratory has recently described the DNA binding properties of FANCI (21, 143). We have found that FANCI is relatively promiscuous in terms of binding to various DNA structures, and that the FANCD2-complexed FANCI exhibits apparently greater affinity toward branched DNA structures in a gel shift assay under non-competitive condition (21). This observation was confirmed by *in vivo* association of FANCI nuclear foci with chromatin and PCNA foci (21). By employing a substrate competition assay, Patrick Sung's group established that FANCI per se recognizes branched structures (143). One explanation for the discrepancy in our respective findings is that the DNA binding assays in these two studies were performed under different reaction conditions. While it may be postulated that a competition assay is more definitive in terms of determining substrate preference, our results unambiguously demonstrate that FANCD2 enhances the selectivity of FANCI toward branched DNA structures through direct interaction *in vitro*.

Because the unmodified FANCI and ID complex recognize branched (fork) structures, it is proposed that the ID complex can be recruited to chromatin or stalled replication forks independently of the FA core complex and regardless of its ubiquitination status (21, 111). This hypothesis does not exclude the possibility that the FA core complex (FANCC, FANCE, and FANCG) may facilitate the recruitment of FANCD2 (ID complex) to sites of DNA damage or stalled replication forks (144, 152, 153). It is conceivable that phosphorylation and monoubiquitination of FANCI and FANCD2 may function to increase ID complex formation and/or its affinity to stalled replication forks (21, 113, 144). In a very recent study using the *Xenopus* egg extract and purified proteins, Knipscheer and colleagues showed that the ID complex binds to chromatin in a manner dependent on DNA replication, DNA damage, and FANCD2 monoubiquitination (154). Additionally, gamma-H2AX, a physiological marker of DSBs, interacts with FANCD2 and is able to facilitate recruitment of FANCD2 to broken DNA ends (136).

4.3. Functions of the ID complex

The branch recognition activity of the ID complex and its co-localization with PCNA in the absence of exogenous DNA damage support the function of FA proteins in stabilizing replication forks during unperturbed S phase and DNA replication (18, 20, 21, 53, 155). When the DNA replication machinery encounters single strand breaks or ICLs, DSBs are likely to be the result (5, 7, 12, 19, 156, 157). FA proteins (including the ID complex) may act to hold together broken DNA ends in the vicinity of the replication site in order to prevent collapse of the replication fork. Subsequent phosphorylation and monoubiquitination of the ID complex, a critical switch that signals initiation of the FA pathway, could then recruit homologous recombination factors, including FANCD1/BRCA2, FANCN/PALB1, FANCJ/BRIP1, BRCA1, and RAD51, to repair DSB and to reestablish the replication fork (66, 139, 140, 158).

The preferential binding activity of the ID complex toward branched structures allows its independent recruitment to chromatin and makes it possible for FANCD2 to act upstream of FANCM phosphorylation (104). FANCD2 has also been shown to be required for efficient XPF-induced incisions around psoralen-generated ICLs (123). However, two recent reports indicate that XPF-ERCC1 precedes FANCD2 foci formation and its recruitment to chromatin, and is required for homologous recombination-mediated DSB repair (159, 160).

It is reasonable to assume that the monoubiquitination of FANCI and FANCD2 could act as a surrogate of PCNA monoubiquitination in the recruitment of UBD- (ubiquitin binding domain) containing TLS polymerases in order to bypass unhooked ICLs. This possibility is supported by a recent study in *Xenopus* egg extract by Johannes Walter's group (154). Through the antibody depletion of FANCD2, they established that the monoubiquitinated ID complex is essential for both incision and TLS bypass, and therefore the overall replication-coupled repair of a site-specific cisplatin ICL

(154). However, it is worth mentioning that another study indicates that the monoubiquitination of FANCI and FANCD2 does not seem to affect TLS-induced mutagenesis in human cells (82).

5. FANCD1, FANCN, AND FANCJ – MUSICIANS

FANCD1, FANCN, and FANCJ are bona fide DSB repair factors. They act downstream of the monoubiquitination of the ID complex in order to mend broken DNA ends produced during replication-coupled ICL repair and to reestablish the replication fork (5, 7, 10, 12, 19). While haplodeficiency of these factors caused by single allelic mutation predisposes humans to breast and ovarian cancers, biallelic mutations cause Fanconi anemia (5, 161).

The connection between Fanconi anemia and DSB repair factors was first shown in an elegant study by Alan D'Andrea's group (48). They established that BRCA2, a factor that facilitates formation of RAD51-ssDNA nucleofilaments (162, 163), is not only mutated in FANCD1 patient (48), but also interacts with monoubiquitinated FANCD2 to form nuclear foci (139, 140). FANCD1 (BRCA2) appears to operate downstream of the FA core complex, but FANCD1/BRCA2 is more important for the repair of replication-blocking lesions relative to the FA core complex (118, 161, 164-168). Although the FANCD1/BRCA2$^{\Delta 27/\Delta 27}$ deficient mice do not recapitulate the bone marrow failure characteristic of FA, their bone marrow cells display more severe spontaneous and crosslinker-induced chromosomal aberrations than the FANCA$^{-/-}$ mice (164, 169).

PALB2, an interacting partner of BRCA2, has been found to be associated with the Fanconi anemia complementation group N (62, 63, 170). FANCN is required for localization of FANCD1/BRCA2 to chromatin and BRCA2-mediated homologous recombination (141, 171, 172). Biallelic mutations in *BRIP1* or *BACH1*, an interacting partner of BRCA1 and an ATP-dependent 5'-3' DNA helicase (137, 173, 174), are responsible for the Fanconi anemia complementation group J (FANCJ) (56, 58, 167). Although not mutated in FA patients, BRCA1 interacts with FANCA, directly binds to the branched DNA structures, and is required for the redistribution of BRCA2 and FANCJ to DNA damage sites (138, 175, 176). BRCA1 was also shown to be required for the FANCD2 nuclear foci formation (64). Using an elegant eChIP (episomal replication-based chromatin IP) system, Lei Li's group has shown that FANCD1/BRCA2, FANCJ/BACH1, and FANCN/PALB2 can be recruited to DNA ICL sites in a replication-dependent and FA core complex-independent manner, suggesting that the stalled replication forks serve as a sufficient signal to initiate homologous recombination-mediated repair (177).

In the absence of the top-tier musicians, second string players such as non-homologous end joining (NHEJ) take over and result in the observed FA phenotype of chromosome instability such as radial chromosomal structures (7, 12, 19, 124, 178).

6. NON-FA FACTORS IN ICL REPAIR – GUEST MUSICIANS

Although not mutated in the FA patients, many other factors are involved in the FA pathway of ICL repair because they resemble the FA phenotype in some aspects such as hypersensitivity to crosslinking agents, hematopoietic defects, and mutagenesis footprints, and/or through their interaction with FA proteins.

6.1. Endonucleases

XPF-ERCC1, a heterodimeric structure-specific endonuclease involved in nucleotide excision repair (NER), is distinct from other NER factors because its deficiency results in uniquely high sensitivity to crosslinking agents (15, 75, 179-183). These observations indicate that XPF-ERCC1 may also be involved in the repair of ICLs. Indeed, purified XPF-ERCC1 protein is able to introduce damage-specific dual incisions on both 5' and 3' sides of the defined psoralen-ICL DNA substrates. The dual incisions take place on the same strand and therefore unhook the ICL (184, 185). Components of the FA core complex and the ID complex are required for the incision (122, 123). More importantly, *ERCC1* deficient mice exhibit certain phenotypes characteristic of FA but not other NER deficiencies, such as hematopoietic defects (186). XPF-ERCC1 also plays an important role in the localization of FANCD2 to chromatin (leading to FANCD2 foci formation) and subsequent homologous recombination-mediated repair (74, 78, 159, 160).

MUS81-EME1 is another member of the XPF/MUS81 family of DNA endonucleases (75). It cleaves 3' flap, replication fork, D-loop, and Holliday junction structures very efficiently (86, 187-191). MUS81-EME1 is likely involved in ICL unhooking (19, 157). However, an unprocessed stalled replication fork is most likely a 5' flap structure and therefore not an ideal substrate for MUS81-EME1. FANCM-FAAP24 remodels the structure of the stalled replication fork through fork regression and can make it into a substrate for MUS81-EME1 (19, 74).

Very recently, mammalian SLX4, a scaffold protein that mediates interactions between endonucleases XPF-ERCC1, MUS81-EME1, and SLX1, was found to be required for the ICL repair (192-195).

6.2. TLS polymerases

Translesion synthesis polymerases are a group of low fidelity DNA polymerases that specialize in bypassing DNA replication-blocking lesions, albeit at a price of elevated mutagenesis (196-198). TLS polymerases REV1 and Pol zeta (REV3-REV7) are required for ICL bypass during ICL repair (16, 78, 82, 83, 199-201). *REV3* deficient mouse embryonic fibroblasts and chicken DT40 cells are extremely sensitive to DNA crosslinking agents (199, 202-204). In chicken DT40 cells, FANCC deficiency and Pol zeta deficiency are epistatic in their sensitivity to crosslinking agents indicating that FANCC and REV1- Pol zeta function in the same ICL repair pathway (83, 199). It also has been shown that the FA core complex is required for efficient REV1 foci formation (82). Pol zeta-depleted

Xenopus egg nuclear extract has been demonstrated to be defective in replication-dependent ICL repair (16). In the context of replication-independent ICL repair, REV1-REV3 also plays a major role in bypassing ICL damage (200).

Additionally, DNA polymerase kappa (DINB1) has been shown to play a role in bypassing a N^2-N^2-guanine ICL *in vitro* and in intact cells (81). Pol eta (XPV) may also be involved in the ICL bypass because the *XPV* deficient cell line XP30RO is hypersensitive to psoralen-induced ICLs but not to psoralen monoadducts (205).

6.3. Mismatch repair factors

Mismatch repair factors MutS beta (MSH2/MSH3), MutL alpha (MLH1/PMS2), and EXO1 also play roles in ICL repair (77-80, 206-208). MutS beta recognizes psoralen ICLs and is required for a repair step prior to engagement of FA proteins in the *in vitro* processing of psoralen ICLs (79, 80, 208). The functional and physical interactions between ERCC1 and MSH2 suggest that MutSβ may also be involved in the incision of ICLs (209). Processing of ICLs by these mismatch repair proteins seems to result in the error-free ICL repair in human cells (208).

MutLα interacts with the helicase domain of FANCJ/BRIP1 and this interaction is required for the repair of ICL because its disruption results in ICL sensitivity (207). Since MutLα is an endonuclease that creates incisions on both sides of a mismatch (210, 211), it is likely that MutL alpha could be involved in the unhooking of ICLs. However, unlike MSH2, MutL alpha deficiency (MLH1 knockdown) results in resistance to psoralen ICLs, suggesting that MSH2 and MLH1 contribute differently to ICL repair (77). Indeed, MLH1 is known to play an important role in activating apoptosis through activation of caspase 3/7, a mechanism which requires DNA fragmentation for its initiation (77).

6.4. Other factors

Bloom (BLM) syndrome shares some phenotypic similarities with FA in terms of hypersensitivity to crosslinking agents, high frequency of chromosomal breaks and rearrangement, and high risk of cancer (84, 212, 213). BLM protein is found to be present in the same BRAFT complex with FA proteins, topoisomerase III alpha and RPA (84). The FA core complex is required for the ICL-induced BLM phosphorylation and assembly into nuclear foci (213). In response to crosslinking agents and replication stress, BLM and FANCD2 are found to colocalize and coimmunoprecipitate with each other (213). FA proteins also collaborate with BLM to prevent chromosome abnormalities during mitosis (214).

The MRN (MRE11-RAD50-NBS1) complex is the major regulator of DNA end processing, and is likely to be involved in the end resection of DSBs produced during ICL repair. In the absence of FANCC, the MRN complex fails to form nuclear foci in response to DNA crosslinking agents, suggesting that MRN may work downstream of the FA core complex (98). NBS1 has also been demonstrated to interact with FANCD2 in response to DNA damage (215), and this interaction is critical for the stability of FANCD2 protein (151).

7. A HYPOTHETICAL MODEL FOR FA PROTEINS IN ICL REPAIR

The primary physiological roles of FA proteins are widely considered to be repair of all forms of replication-stalling factors (bulky DNA lesions, secondary structures, strand breaks, ICLs, and etc) in order to prevent deleterious collapse of the replication fork, to restart replication after repair, and therefore to maintain the stability and integrity of DNA replication. Using the ultimate replication-blocking lesion, namely ICLs, as an example, we summarize what we have learned about the FA repair pathway as follows. We propose that the repair pathway involves four steps: (1) damage recognition, (2) ICL unhooking, (3) ICL bypass, and (4) fork reestablishment. Because FANCM and the ID complex recognize branched structures, they are likely to be involved in recognition of the ICL-stalled replication fork (Figure 1A). The stalled replication fork also activates the ATR-CHK1 kinases (damage response) which subsequently phosphorylate the FA core and ID complexes. The activated FA core complex monoubiquitinates the ID complex through its FANCL ubiquitin ligase activity and thereby initiates repair of the damaged replication fork.

The mechanism of the subsequent ICL unhooking step remains elusive. There are likely two processes which are able to unhook ICLs. One is by action of MUS81-EME1 and XPF-ERCC1 on the leading strand (Figure 1B). For MUS81-EME1 to be able to make incision, the stalled replication fork has to be remodeled by FANCM-FAAP24 through its branch point translocase activity (19), because MUS81-EME1 does not cut the 5' flap structure that is usually seen in a regular replication fork. The monoubiquitinated ID complex may recruit BRCA1-FANCJ helicase or other helicases to unwind the duplex locally in order to make the other side of the stalled replication fork suitable for the incision by the XPF-ERCC1 endonuclease (10, 19). In this scenario, the FA core complex and attendant helicases may mimic the action of transcription factor TFIIH in nucleotide excision repair. Accordingly, the entire FA core complex may be directly interacting with the damaged DNA (in addition to FANCM-FAAP24) by participating in the maintenance of the opened bubble DNA structure.

The unhooked ICL lesion is then bypassed by TLS polymerases such as REV1 and Pol zeta (Figure 1C). One caveat to keep in mind is that for ICL unhooking on the leading strand, the XPF-ERCC1 incision has to take place prior to TLS in order for an extendable 3' end to be available for DNA synthesis. Components of the FA core complex and FANCJ helicase may facilitate the subsequent bypass activity. The multi-point DNA binding activity of the monoubiquitinated ID complex (or FANCM-FAAP24) may then help to hold together the 'collapsed' end in the vicinity of the processed fork for subsequent repair. The ID complex may also recruit double strand break repair factors

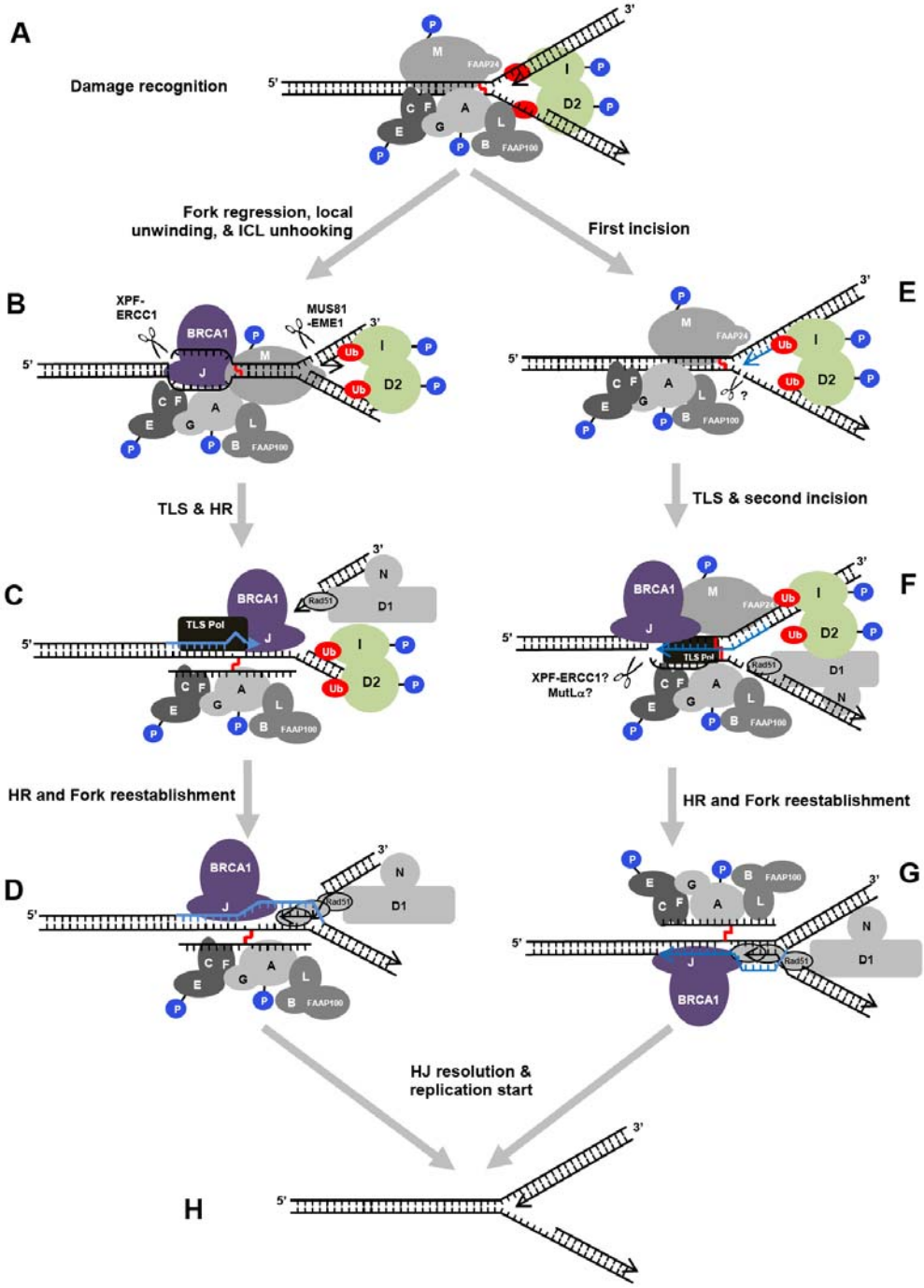

Figure 1. The Fanconi anemia pathway of ICL repair. A, a stalled replication fork can be recognized simultaneously by FANCM-FAAP24, ID complex, other unidentified FA factors, or combination of these factors. FANCI and FANCD2 are depicted to be present in the ID complex after their phosphorylation and monoubiquitination, but do not necessarily need to be continuously together in order to exert their functions. B, ICLs are unhooked by XPF-ERCC1 and MUS81-EME1. C, Translesion synthesis across the unhooked ICL. D, The replication fork reestablishes through homologous recombination. E, An alternative way of ICL unhooking via the function of an unidentified 5' flap endonuclease. F, Translesion synthesis and a second incision to completely unhook an ICL. G, Fork reestablishment through homologous recombination. H, DNA replication restarts after resolution of the produced Holliday junction. Red zigzag line: ICL. Letter 'P' in a blue circle: Phosphorylation; Red ovals: monoubiquitination; All other letters in circles represent different Fanconi anemia complementation groups. Factors that are likely to be present in a subcomplex are shown by a common color. Scissors: endonucleases. Newly synthesized strands are indicated in light blue.

such as BRCA1) to maintain integrity of the processed replication fork.

Replication fork reestablishment may be achieved through recruitment of the RAD51 recombinase (facilitated by FANCD1/BRCA2-FANCN/PALB2) to single-stranded 3' overhang followed by assembly of a nucleofilament for strand invasion (annealing with newly synthesized strand) (Figure 1D). Further end resection can be accomplished by the MRN complex (98, 151, 215) with the BRCA1-FANCJ helicase assisting in strand invasion by unwinding dsDNA. This process can take place in the presence of the unhooked ICL moiety and components of the FA core complex may participate in the process.

Alternatively, as observed in the *Xenopus* extract, ICL incision can take place on the lagging strand (Figure 1E) (16, 154). MUS81-EME1 functions as a 3' flap endonuclease and is unlikely to be involved in this first incision because of its substrate specificity (75, 187, 188, 216, 217). We speculate that an unidentified 5' flap endonuclease is involved in this lagging strand incision with FA proteins coordinating its function for precise incision.

In this second scenario, as illustrated by Johannes Walter's group, DNA synthesis on the leading strand provides a convenient primer end for lesion bypass and incision is not required for TLS to take place (Figure 1F) (16). XPF-ERCC1 could be the endonuclease for the second incision as it incises on both sides of a psoralen ICL (184). MutL alpha is another likely candidate to make such incision. The FA core complex and/or FANCJ could help to make the incision specific to the ICL.

Without much end resection (by MRN complex, for example), the resulting one-ended DSB with a 3' overhang could serve as a primer to reestablish the replication fork through strand invasion (i.e. annealing with the parental strand), a process catalyzed by RAD51 and FA proteins (Figure 1G).

The preferential Holliday junction binding activity of FANCI and the ID complex may help to recruit resolvases in order to allow DNA replication to restart following resolution of the resulting Holliday junction (Figure 1H). It is conceivable that the unhooked ICL moiety could then be removed by the full NER machinery after replication.

8. CONCLUSION

In summary, the FA pathway of DNA repair is the most complicated and least understood repair mechanism. In fact, a more accurate name to describe this repair mechanism could be the "Fanconi anemia network of DNA repair". Although many questions still remain answered, it is clear that Fanconi anemia is a bona fide DNA repair disorder. The biased distribution of the disease genes in FA patients (85% being *FANCA*, *FANCC*, or *FANCG*, and 5% being the DNA-interacting *FANCM*, *FANCI*, *FANCD2*, and *FANCJ*) indicate on one hand that FANCA, FANCC, and FANCG are involved in processes other than DNA repair in the FA etiology. On the other hand, FANCA, FANCC, and FANCG could be directly involved in critical DNA repair transactions.

One difficult but interesting issue is that many FA proteins do not have identifiable domains to indicate how they contribute to biological processes including DNA repair. Future research focusing on exploring the biochemical properties of FA proteins and mapping out the dynamic protein-DNA and protein-protein interaction network should be promising in terms of delineating how FA proteins participate in the DNA damage repair and the maintenance of genome integrity.

A greater elucidation of FA protein –mediated repair mechanisms will not only be useful for FA diagnosis and intervention, but also provide a meaningful basis towards understanding how to overcome drug resistance during cancer chemotherapy. It appears that ICLs represent the primary cytotoxic lesion induced by clinically important bi-functional chemotherapeutic agents, such as mitomycin C, cisplatin, psoralen, nitrogen mustards, and nitrosourea (43, 74, 218, 219). Cancer cells develop resistance to such agents by up-regulation of the FA pathway after initial treatment and therefore compromise subsequent therapeutic efficacy. Development of small inhibitory molecules against FA proteins may help potentiate toxicity of the drugs toward cancer, reduce dosage of treatment, and minimize drug-related side effects.

Small molecule inhibitors targeting FA proteins will have implication in cancer treatment through synthetic lethality which is an emerging therapeutic strategy to effectively treat cancers while sparing normal cells and tissue. Cancer cells that arise as a result of deficiencies in one DNA repair pathway may depend heavily on other repair pathways for survival. Inactivation of such secondary repair pathways prove to lethal for these cancer cells (12). For example, inhibition of an auxiliary base excision repair protein, PARP1, causes synthetic lethality in breast and ovarian cancer cells with BRCA1 and BRCA2 (homologous recombination repair) deficiency (220-222). Similarly, abrogation of the ATM pathway was found to cause synthetic lethality in tumors with FA deficiency, suggesting that ATM inhibitors might be the next generation drugs to be used for treatment of cancers that arise in FA patients (12, 223).

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Abbreviations: FA: Fanconi anemia; ICL: interstrand crosslink; MMC: mitomycin C; DEB: diepoxybutane; ID: FANCI-FANCD2; ATR: ataxia telangiectasia and Rad3-related; MRN: MRE11-RAD50-NBS1; TLS: translesion synthesis; NER: nucleotide excision repair; MMR: mismatch repair; HR: homologous recombination; ROS: reactive oxygen species

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Send correspondence to: Yanbin Zhang, Gautier Bldg/Rm 310, University of Miami School of Medicine, 1011 NW 15th Street, Miami, FL 33136, Tel: 305-243-9237, Fax: 305-243-3955, E-mail: yzhang4@med.miami.edu

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