Mutat Res Fund Mol Mech Mutagen xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Mutat Res Fund Mol Mech Mutagen

journal homepage: www.elsevier.com/locate/mut

Review

Beyond interstrand crosslinks repair: contribution of FANCD2 and other Fanconi Anemia proteins to the replication of DNA

Q1 Maria B. Federico [1], Paola Campodónico [1], Natalia S. Paviolo [1], Vanesa Gottifredi *

Cell Cycle and Genomic Stability Laboratory, Fundación Instituto Leloir-Instituto de Investigaciones Bioquímicas de Buenos Aires-Consejo Nacional de Investigaciones Científicas y Técnicas, Argentina

ARTICLE INFO

Article history:
Received 16 June 2017
Accepted 11 September 2017
Available online xxx

Keywords:
Homologous-directed repair
Translesion DNA Synthesis
Non-homologous end joining
BRCA1
BRCA2

ABSTRACT

Biallelic mutations of FANCD2 and other components of the Fanconi Anemia (FA) pathway cause a disease characterized by bone marrow failure, cancer predisposition and a striking sensitivity to agents that induce crosslinks between the two complementary DNA strands (inter-strand crosslinks-ICL). Such genotoxins were used to characterize the contribution of the FA pathway to the genomic stability of cells, thus unravelling the biological relevance of ICL repair in the context of the disease. Notwithstanding this, whether the defect in ICL repair as the sole trigger for the multiple physiological alterations observed in FA patients is still under investigation. Remarkably, ICL-independent functions of FANCD2 and other components of the FA pathway were recently reported. FANCD2 contributes to the processing of very challenging double strand ends (DSEs: one ended Double Strand Breaks -DSBs- created during DNA replication). Other ICL-independent functions of FANCD2 include prevention of DNA breakage at stalled replication forks and facilitation of chromosome segregation at the end of M phase. The current understanding of replication-associated functions of FANCD2 and its relevance for the survival of genomically stable cells is herein discussed.

Contents

Abbreviations: A-EJ, alternative end joing; APH, aphidicolin; BIR, break induced replication; BTRR, BLM helicase/topoisomerase IIIa (TOPOIIIa)/RMI1 and RMI2 cofactors; CFS, common fragile sites; Cis, cisplatin; DEB, diepoxybutane; DSBs, double strand breaks; DSEs, one ended DSBs; FA, fanconi anemia; FAPP, FA associated proteins; HDR, homologous-directed repair; HSC, haematopoietic stem cells; HU, hydroxyurea; ICL, inter-strand crosslinks; MMC, mitomycin C; MMS, methyl methane sulfonate; NER, Nucleotide Excision Repair; NHEJ, non-homologous end joining; PICH, PLK1-interacting checkpoint helicase; RF, replication fork; ssDNA, single stranded DNA; TLS, traslesion DNA Synthesis; UFB, ultra-fine DNA bridges; UV, ultraviolet; 53BP1, p53-binding protein 1.

* Corresponding author.
E-mail address: vgottifredi@leloir.org.ar (V. Gottifredi).
[1] Equal contribution to this work.

http://dx.doi.org/10.1016/j.mrfmmm.2017.09.004
0027-5107/

1. Fanconi anemia: the disease

Fanconi anemia (FA) is a rare recessive disorder with an incidence of 1–5 per 1,000,000 births [1]. Despite such apparent low frequency, FA is the most common inherited bone marrow failure syndrome [2]. While FA is classified as an anemia, the initial signs of the illness may include bone or skeleton defects, renal dysfunction, short stature and very frequently abnormal hyper- and hypo-pigmentation of the skin and café_au_lait spots [3,4]. However, the disease may not be diagnosed until the onset of pancytopenia (reduction in the number of cells of all haematopoitic linages) [2]. The syndrome is also characterized by a predisposition to blood cancers such as myeloid leukemias, and other type of cancers such as squamous cell carcinomas [2,5,6]. Furthermore, bone marrow transplantation in these patients is challenging as all tissues are extremely sensitive to ICL-generating therapy [7,8]. In fact, the modification of transplantation therapies in FA patients correlates with an improvement in their life expectancy, which has increased from 33 years to patients currently reaching their 40 s and even their 50 s (Fanconi Anemia Research Fund) [9].

At least 5 decades after the discovery of the illness, the first FA gene, FANCC, was identified [2,10]. To date 22 FA genes are known and it is possible that new genes will be discovered in the future. The manifestation of the disease requires the germline inactivation of both alleles of one of the genes in the FA pathway. The FA family complementation groups are: FANCA, FANCB, FANCC, FANCD1, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCJ, FANCL, FANCM, FANCN, FANCO, FANCP, FANCQ, FANCR, FANCS, FANCT, FANCU, FANCV and FANCW [2,11–13]. In all cases, the elimination of each gene product enhances ICL sensitivity [3].

The characterization of the different clinical manifestations in FA patients has shed light on the aetiology of the illness in each genetic background. Patients with germline biallelic inactivation of 17 bona fide FA genes (FANCA, FANCB, FANCC, FANCD1 (BRCA2), FANCD2, FANCE, FANCF, FANCG, FANCI, FANCJ (BRIP1), FANCL, FANCN (PALB2), FANCP (SLX4), FANCQ (XPF), FANCT, FANCU (XRCC2), FANCV (Rev7) and FANCW (RFWD3) suffer from bone marrow failure and the predisposition to leukaemia and other cancers, including squamous cell carcinoma (head and neck, gynaecological), and oesophageal, liver, brain, skin and renal tumours [14,15]. In contrast, patients carrying mutations in FANCO (Rad51C), FANCR (Rad51) and FANCS (BRCA1) can be affected by other types of cancer including breast cancer, but they do not develop bone marrow failure and leukaemia. They were therefore classified as FA-like syndromes [16,17]. In some cases, patients with germline mutations in a given FA gene are rare. For example, only hypomorphic mutations for BRCA1 were identified in 2 patients [18,19]. Finally, FANCM cannot be classified in these categories as only one patient carrying mutations on both FANCM and FANCA genes has so far been described [20]. As wild type FANCM does not complement the ICL sensitivity of such cells, the contribution of FANCM loss to the illness is unclear. Also, no patients with biallelic mutations of the FA Associated Proteins; FAAP16, FAAP20, FAAP24 and FAAP100 or the deubiquitylating enzyme, USP1, have been described so far. While such limitations preclude a conclusive analysis, it is expected that more data will facilitate the association of different aspects of the disease with specific functions of a protein/s within the FA pathway. For a more extensive analysis refer to references [3,21].

2. The contribution of FANCD2 and other FA proteins to the repair of intra-strand crosslinks between Watson and Crick DNA strands

2.1. Mechanistic insights

ICLs are DNA lesions that covalently link the Watson and Crick strands. Some chemotherapeutic agents such as mitomycin C (MMC), diepoxybutane (DEB) or cisplatin (Cis) cause ICLs accumulation and cells derived from FA patients are strikingly sensitive to such compounds [2,3,22].

ICL removal by the FA pathway is generally accomplished in a manner that is strictly dependent on DNA replication. In fact, ICL repair initiates when the replication fork (RF) abuts the DNA lesion. The FA pathway triggers nuclease-dependent unhooking of the ICL (Supplementary Fig. 1 A–F), DNA synthesis across the ICL-bound DNA template, and homologous-directed repair-HDR (Supplementary Fig. 1F). The mechanisms of DNA synthesis across DNA lesions and HDR steps are shown in Supplementary Figs. 2 and 3 respectively. For a complete revision see [2,23].

2.2. Biological relevance

2.2.1. Genomic stability and cell survival

Elimination of each FA protein causes aberrant processing of the ICLs, which in turn triggers accumulation of aberrant chromosomes and cell death [24–28]. Such type of genomic instability could be caused by the dysregulated processing of ICL-repair intermediates by NHEJ (non-homologous end joining), a pathway that ligates double strands breaks without any homology requirement (DSBs) [29]. The causal relationship between the loss of FANCD2 and the dysregulation of NHEJ has been explored in human and mouse cells and in the *C. elegans* worm model [24,25,28]. Conclusions are so far contradictory as NHEJ inhibition/inactivation was reported to revert or increase the cell death and the genomic instability caused by the elimination of FA proteins [24,25,28]. Further experimentation is required to evaluate the potential of NHEJ as a druggable target in the context of the treatment of tumors with FA deficiencies. However and despite the lack of consensus, it is clear that the DSB pathway choice influences the accumulation of chromosomal abnormalities and the survival of cells depleted from FA proteins.

2.2.2. Bone marrow failure

The massive failure of all blood cell lineages in FA patients suggests that the loss of haematopoietic stem cells (HSCs) may be the trigger for the bone marrow failure (BMF) [30]. In fact, the reduction in HSCs precede the clinical manifestation of BMF in FA patients [31]. To restore depleted blood cells, quiescent HSCs re-enter the cell cycle causing massive activation of the metabolism which in turn generates reactive oxygen species (ROS)-mediated DNA damage. In the absent of a functional FA pathway, the deficiency in DNA repair triggers p53/p21 hyperactivation and HSC cell death [31,32].

It is unlikely that exogenously induced ICLs are the trigger for such massive bone marrow defect, as FA patients are not normally exposed to clastogenic agents. A potential endogenous source of FA-activating DNA lesions are small aldehydes such as formalde-

Please cite this article in press as: M.B. Federico, et al., Beyond interstrand crosslinks repair: contribution of FANCD2 and other Fanconi Anemia proteins to the replication of DNA, Mutat Res Fund Mol Mech Mutagen (2017), http://dx.doi.org/10.1016/j.mrfmmm.2017.09.004

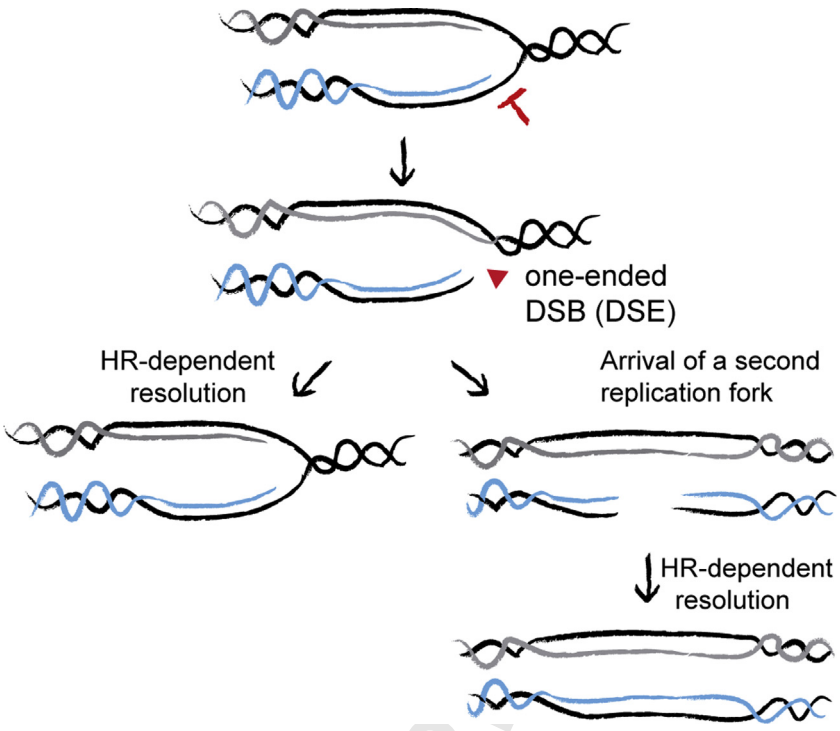

Fig. 1. DSE formation and resolution.
DSE are genetated by the abusting of RFs with nicks in one DNA strand or after the processing of collapsed RFs.They require HDR for resolution. However it is unclear if and how the replisome can be reassembled in HDR-repaired RFs. A second RF arriving from the other side of the DSE may be required for its HDR-mediated resolution and/or for the finalization of DNA replication at those DNA regions.

hydes and acetaldehydes [30]. While acetaldehydes were shown to stimulate monoubiquitylation of FANCD2 [33], cells derived from FA patients are sensitive to both formaldehydes and acetaldehydes [34–37]. Tissues with low levels of detoxifying enzymes ALDH2 and ADH5, e.g. the hematopoietic lineage, rely heavily on the FA pathway to process DNA lesions generated from endogenous aldehydes [34,38]. In adittion, Aldh2(-/-) Fancd2(-/-) and Adh5-/-Fancd2 -/- mutant mice closely recapitulate the defects hematopoietic defects observed in FA patients [38,39]. Together these results have built a strong case linking defects in the processing of specific endogenous byproducts with bone marrow failure in FA patients. However, whether the defects in ICL repair represent the sole trigger for genomic instability and tumorigenesis in FA patients is still a subject of intense investigation. FA cells are also sensitive to ReactiveOxygen Species (ROS) as extensively discussed in [40,41].

3. The contribution of FANCD2 and other FA proteins to the repair of Double Strand Breaks

3.1. Mechanistic insights

In cells, DSBs can accumulate independently of ICLs. γIR and X-rays are sources of direct (not associated with replication) DSBs that are most frequently used in experimental models and for treatment of patients. DSBs are dangerous because the disruption of both DNA strands is very challenging to the stability of the genome [42]. A subtype of DSB relevant to this discussion are single-ended double strand ends (DSEs). (Fig. 1). DSEs can be generated by endonucleases when persistently stalled forks lose their ability to replicated (collapsed RFs) or when replication forks encounter nicks in the template strand [43–45]. At DSEs, RFs may be reconstituted by HDR and other mechanisms that repair canonical, double ended DSBs (Fig. 2). It is unclear if such RFs could be proficient in DNA replication as the replisome may completely dissociate both from collapsed RFs and DSEs. It is therefore possible that the repair of DSE require the abutting of a second RF (Figs. 1 and 2). Alternative, replisomes may not completely dissociate from DSEs as reported at DSE generated by methyl methane sulfonate (MMS) treatment [46].

The repair of DSEs and of two-ended-DSBs may be differentially regulated. In fact, the FA pathway is much more relevant for the processing of DSEs than for the repair of DSBs. Upon γIR, a well-characterized source of replication-independent DSBs, the ATM kinase activates FANCD2 by phosphorylation and FANCD2 localizes to sites of DNA damage [47]. Nevertheless, the contribution of FANCD2 to the cellular response to γIR seems to be tangential as FANCD2-deficient cells are only moderately sensitive to both γIR and X-rays [48–51]. In addition, FANCD2 contributes only mildly to the repair of site-specific DSBs generated by restriction enzymes [52]. Conversely, FANCD2 is key to the resolution of ICL-dependent replication-coupled DSEs [53]. These results led to the assumption that FANCD2 is specifically required for the resolution of replication-coupled DSEs but not direct DSBs.

Compelling evidence has demonstrated that the FA pathway is required for the processing of DNA replication-associated DSBs generated at ICL (Fig. 3A). However, the role of FA proteins in the processing of replication-associated DSEs generated by sources other than ICL-processing is less understood. Prolonged exposure (24 h) to the inhibitor of ribonucleotide reductase, hydroxyurea (HU) caused accumulation of replication associated DSEs [43,54]. In that scenario, Rad51 (FANCR) nuclear foci were detected and were interpreted as sites of HDR-directed repair of broken RFs [43,55]. Furthermore, in such experimental settings, Rad51 depletion steeply delayed the repair of DSEs [43]. FANCD2 is also recruited to replication factories after HU treatment but its role in the repair of HU-triggered DSEs has not been reported. Notwithstanding this, the contribution of FANCD2 to the repair of DSEs which are generated independently from ICLs processing has been explored in the context of DNA lesions generated after Ultraviolet irradiation(UV) [56]. It has long been known that UV irradiation

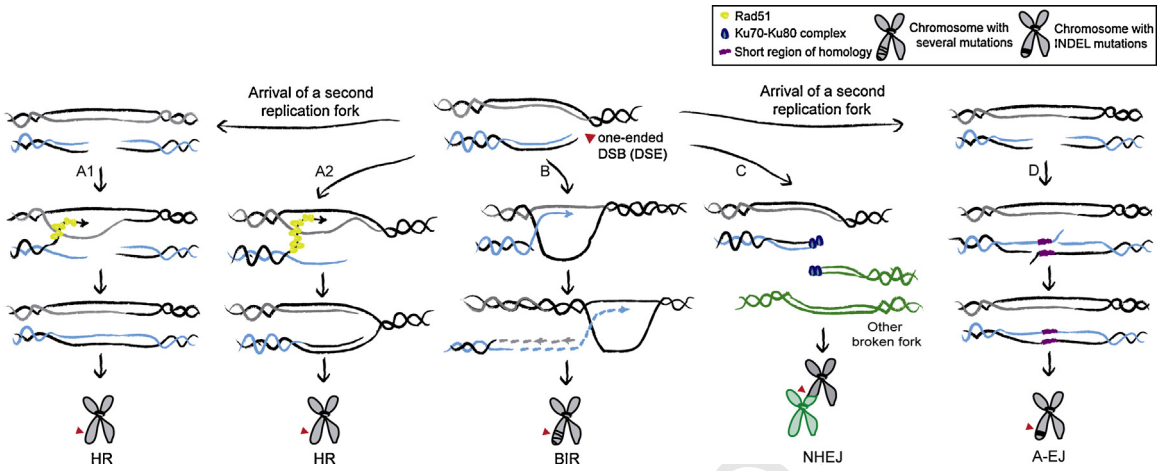

Fig. 2. Mechanism of resolution of DSEs.
A) Classical HDR can restore RFs structural integrity at convergent (A1) or individual (A2) replication forks. B) Alternatively, another type of HDR, break-induced replication (BIR), can resolve DSEs in an error prone manner that involves extensive and mutagenic DNA synthesis. However, it is preferentially used after oncogenic stress [79]. The key step that commits a DSE to HDR (in A and B) is the generation of protruding ends by resection, and their coating with Rad51 filaments on ssDNA. During HDR (A and B), the template for DNA synthesis is the homologous DNA strand, primarily the sister chromatid. C) The resolution of DSE by NHEJ causes aberrant fusion of non-homologous crhomosomes. D) A-NHEJ (alt-NHEJ) requires microhomology, i.e., a few bp sequence identity between the DNA ends. Deletions are introduced in the DNA sequence flanking the homologous region. For all panels: in the chromosome, the original localition of the DSE is indicated with a red arrow. The black lines in chromosomes represent point mutations or micro deletions/insertions.

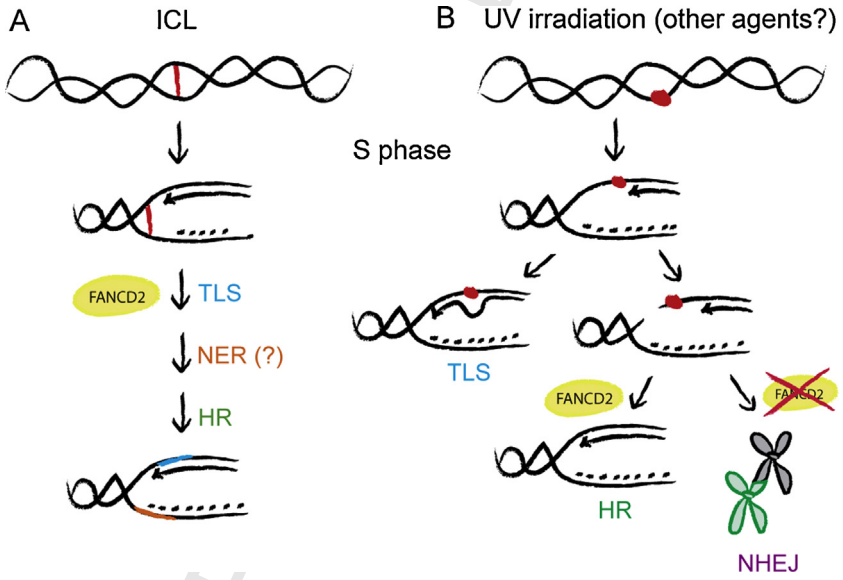

Fig. 3. FANCD2 as a facilitator of HDR-mediated resolution of DSEs.
A) During ICL repair FANCD2 coordinates TLS, HDR and possibly NER. The coordinating role of FANCD2 is not required after other type of DNA lesions and therefore the function of the FA pathway may be limited to ICL repair. B) After UV irradiation, TLS take place at proficient, not collapsed RFs while FANCD2-triggered HDR are events take place at RF that collapsed into DSEs. Loss of FANCD2 results in dysregulated processing of DSEs by NHEJ. Because DSEs may be generated by genotoxins other than UV irradiation, the facilitation of HDR may be a function of the FA pathway that preserves genomic stability after a plethora of genotoxins.

causes the monoubiquitylation of FANCD2 and its recruitment to replication factories [57]. However, the role of FANCD2 in the cellular response to UV irradiation was not further evaluated as cells depleted from FANCD2 and other FA proteins are not sensitive to UV irradiation [20,56–64]. In addition, FA proteins seem dispensable after UV irradiation, as the coordinated activation of Translesion DNA Synthesis (TLS) and HDR is not necessary to repair UV-triggered DNA lesions in S phase (Fig. 3B). While the contribution of TLS to the replication of UV-damaged DNA has been extensively documented [65], the role of HDR in such response is less understood. While initial predictions suggested that DSBs should not be generated after UV irradiation, DSBs accumulation was detected even after moderate UV irradiation [56,66–68]. Such DSBs are most likely DSEs as the are associated with DNA replication and cause an increase the HDR-dependent exchange of sister chromatids [56]. While the levels of UV-induced DSEs are not regulated by FANCD2, its ubiquitylation (and therefore other upstream components of the FA pathway) regulates the DSE repair pathway choice, specifically preventing the aberrant activation of NHEJ at DSEs (Fig. 3B) [56]. Because many other genotoxic treatments generate indirect DSEs during S phase, it is possible that FANCD2 facilitates HDR, preserving chromosome integrity after an unanticipated broad range of DNA damaging agents (see Section 3.3).

Another inducer of FANCD2 monoubiquitylation is BRCA1/2 depletion [69,70]. In such scenario, FANCD2 acts as a backup regulator of DSE repair promoting the survival of BRCA1/BRCA2 deficient cells [69,71]. Because in such genetic backgrounds HDR cannot be activated, FANCD2 facilitates the activation of other DSB repair

Please cite this article in press as: M.B. Federico, et al., Beyond interstrand crosslinks repair: contribution of FANCD2 and other Fanconi Anemia proteins to the replication of DNA, Mutat Res Fund Mol Mech Mutagen (2017), http://dx.doi.org/10.1016/j.mrfmmm.2017.09.004

mechanisms. Specifically, FANCD2 aids pol θ loading onto DNA, favoring the microhomology searching step of alternative end joing (A-EJ) [70]. This is an error-prone "backup" pathways that uses small homologous sequences of a few base pairs to align broken ends before joining, thereby deleting flanking regions in close proximity to the original break [72]. The involvement of FANCD2, pol θ and PARP1 in A-EJ activation was demonstrated using a cell-based assay that measures the efficiency of recombination of two GFP alleles (A-EJ assay) [69,70]. Because of the need for microhomology search, It is possible that the resolution of DSEs by A-EJ requires the abutting of a second fork coming from the opposite direction [72] (Fig. 2D). While more investigation is required to fully understand the mechanism by which FANCD2 promotes A-EJ, it is clear that FANCD2 has a dual role in the choice of a DSB resolution pathway: it contributes to HDR in cells proficient for BRCA1/2, but it also promotes A-EJ, a role that is exacerbated in cells deficient in BRCA1/2.

3.2. Biological relevance

Depletion of FANCD2 in UV-irradiated samples prevents sister chromatid exchange and causes the accumulation of micronuclei and aberrant chromosomes including radial chromosomes [56]. Remarkably, chromatidic aberrations and micronuclei were not detected in cells co-depleted from FANCD2 and XRCC4, a component of the NHEJ pathway [56]. None of these genetic modifications modulate cell survival, hence suggesting that the oncogenic drive of FANCD2 depletion in this scenario is high, as it exclusively modulates genomic stability parameters. To prevent NHEJ activation after UV irradiation FANCD2 requires lysine 559, which is the target of monoubiquitylation by the FA core complex. Thus, the canonical FA pathway is required to protect genomic stability after UV irradiation. Remarkably, such function of FANCD2 may be also relevant during the cellular response to other non-ICL inducing agents that were reported to activate FANCD2, for example HPV16 E6/E7 expression [73], aphidicolin-APH or HU treatments [74–76], PARP inhibition [71] and R loop accumulation [77]. Given that genomic instability does not increase in UV-treated FANCD2/XRCC4 depleted samples, the potential of NHEJ inhibitors could be evaluated as antioncogenic agents that could be used to treat FA patients. However, at least two cautionary remarks should be taken into consideration. First, NHEJ cannot be inhibited globally as it is required for telomere processing [78]. Second, other types of DSE resolution pathways such as Break Induced Replication (BIR), which can be very mutagenic [79] could be used with increased frequency after inhibition of NHEJ.

While FANCD2 promote HDR in BRCA2 proficient backgrounds, in BRCA2 deficient cells it facilitates the alternative DSE resolution by A-EJ [69–71]. Mutational signatures associated with the dysregulated utilization of Pol θ- and possibly FANCD2- were documented after BRCA1 and BRCA2 depletion [80,81]. While such signatures suggest dysregulation of A-EJ in such HDR deficient backgrounds, they do not rule out the participation of other mechanisms during the resolution of DSEs. For example, NHEJ can also join DNA ends with long 50nt overhangs, giving rise to junctional microhomology [82]. The elimination of FANCD2 further modulates the already altered DSE repair pathway choice of BRCA2 depleted cells. Combined elimination of FANCD2 and BRCA2 increases the number of chromosomal aberrations in cells treated with PARP inhibitors [71]. It is unclear if such genomic instability is associated with a change in the DSE repair pathway choice, perhaps involving increased NHEJ-mediated resolution of such DNA lesions but it is likely associated with a downregulation of A-EJ triggered by FANCD2. Moreover, in BRCA1/2 depleted cells, FANCD2 elimination also reduces cell survival suggesting that A-EJ protects BRCA2 depleted cells from cell death [69,70]. Co-depletion of FANCD2 and Pol θ causes embryonic lethality in mice [70]. While such results reveal a cell survival promoting activity of FANCD2 in BRCA2 deficient backgrounds, the also suggest that FANCD2 and Polθ functions do not fully overlap. It is possible that FANCD2 may be a poor inducer of A-EJ in HDR proficient backgrounds but an efficient inducer of such type DSE in BRCA2 deficient (and possibly other HDR deficient) cells. In any case, when considering the relative mutagenic load of each DSE repair pathway, it should be kept in mind that while A-EJ is indeed error-prone choice, HDR can also be mutagenic at DSEs [83]. In such scenario, FANCD2 arises as a factor that regulates the degree of genomic alteration associated with the repair of such intrinsically mutagenic DNA lesions.

4. Contribution of FANCD2 and other FA proteins to the prevention of DSE formation

4.1. Mechanistic insights

The encounter of a RF with a replication barrier causes multiple changes in the RF structure or dynamics which may regulate RF collapse and DSE formation. Many genotoxic agents including topoisomerase inhibitors, ICL-inducing agents, DNA synthesis inhibitors, and base-damaging agents increase the size of single stranded DNA (ssDNA) stretches at the tip of RFs [84–86]. Rad51 (FANCR) protects such ssDNA regions, preventing the uncoupling of parental DNA at the tip of the fork [85] and promoting the formation of reversed RFs (Fig. 4A) [84]. The latter four-way junction DNA structures are generated after the annealing of the two newly synthesized strands and the re-annealing of the two parental strands [87]. Reversed RFs are formed with high frequency (20–30% of all forks) after treatment with different genotoxic agents [84] aiding DNA repair, DNA damage tolerance events and checkpoint activation [84,88–92]. Moreover, in the context of persistent DNA replication blocks, the structure of reversed forks may be less fragile than the typical three-way junctions forks, preventing RF breakage [91,93] and protecting asymmetric nascent DNA ends [94]. Pathways involved in RF reversal and restoration were identified and are discussed elsewhere. Another transaction reported at RFs is repriming, as documented in Rad51-depleted cells treated with UV irradiation (Fig. 4B) [95]. In summary, a number of adaptative events that reverse, stabilize or promote the maintenance of DNA replication are required to prevent RF collapse and breakage and severals FA proteins are involved in such events [87].

Because the nascent DNA arm of a four-way junction resembles a DSB, such arm may also require protection from DNA processing. In agreement with such prediction, recruitment of BRCA1, BRCA2 and FANCD2 were reported to prevent the MRE11 exonuclease-mediated processing of nascent DNA after HU and APH treatment [76,85,94,96,97]. In the absence of FANCD2 monoubiquitylation, severe nucleolytic degradation was shown to depend on the concerted action of both MRE11 an another nuclease, FAN1 (Fig. 4C) [74,98]. Intriguingly, MRE11-triggered nascent DNA degradation was revealed also when Rad51 function was impaired [76,85,92,95]. Since Rad51 depletion prevents fork reversal [84,92], it has been proposed that MRE11 attacks non-reversed forks [92]. In that case the substrates for MRE11 exonuclease activity could most likely be ssDNA structures formed behind replication [85,95]. In fact, after MMS treatment, ssDNA gaps but not ssDNA stretches were reduced by the inhibition of MRE11 exonuclease activity [85]. Likewise, a more recent study reported that in UV irradiated human cells, Rad51 depletion triggers MRE11-dependent degradation of ssDNA behind the fork but not of ssDNA stretches at the fork [95].

Not only the pathological, but also the physiological processing of RFs by exonucleases has been reported. In the context of a proficient FA pathway, MRE11, FAN1 and DNA2 were reported

Please cite this article in press as: M.B. Federico, et al., Beyond interstrand crosslinks repair: contribution of FANCD2 and other Fanconi Anemia proteins to the replication of DNA, Mutat Res Fund Mol Mech Mutagen (2017), http://dx.doi.org/10.1016/j.mrfmmm.2017.09.004

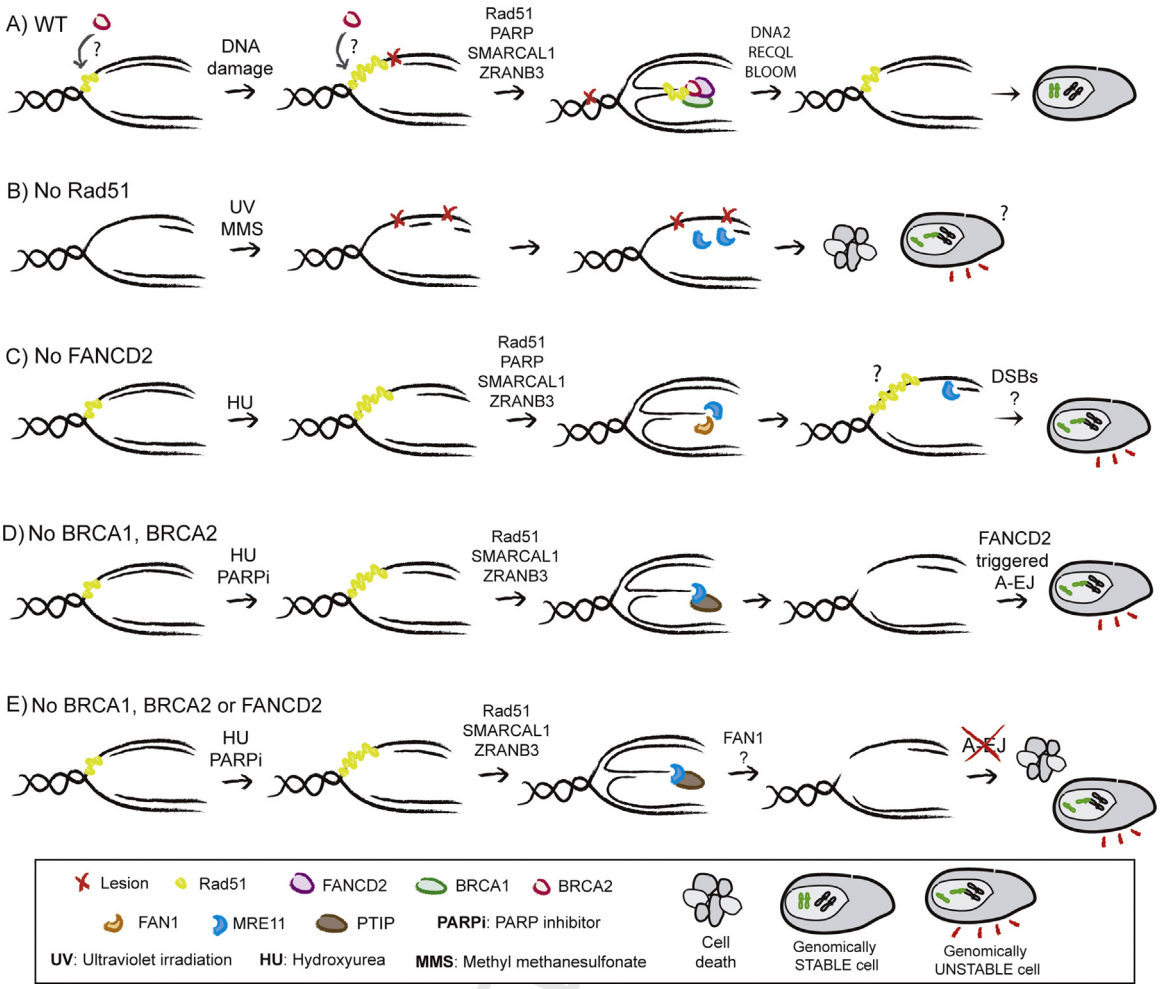

Fig. 4. RF adaptation to damaged templates.
A) Rad51 localizes to RFs, probably at ssDNA stretches and at the tip of the fork. When RFs encounter DNA lesions, the size of the ssDNA stretch increases perhaps augmenting the loading of RAD51, and thereby facilitating RF reversal [84]. Rad51 is unloaded at reversed forks, which are poor in ssDNA. It is unknown if BRCA2 aids RF reversal by Rad51. Other factors such as PARP, SMARCL1, and ZRANB3 promote the generation of reversed forks. Such four way DNA structures may facilitate the relocation of the DNA lesion to DNA-repair prone regions of the DNA. ssDNA regions accumulate at the tip of the reversed fork in a manner that depends mainly on the asymmetry between both strands. BRCA1, BRCA2 and FANCD2 protect the DNA ends from nascent DNA degradation. Reversed forks are re-converted into typical three-way junction structures by RECQ1, DNA2 and BLOOM. Replication-competent RFs finish DNA synthesis, promoting the proliferation of genomically stable cells. B) In the absence of RAD51, RFs accumulate two types of ssDNA regions: ssDNA stretches and ssDNA gaps behind the fork [85,95]. Fork reversal does not take place without Rad51 [84]. Non-reversed RFs are subject to nucleolytic degradation by MRE11 and the replication program is altered by facilitated repriming. Fragile RFs collapse and cell death increases [95]. Genomic instability could also increase but has not been reported to date. C) In the absence of FANCD2 it has been proposed that reversed RF accumulate [76] in cells expressing Rad51 albeit the model has been challenged [92]. Unprotected reversed forks are subjected to dysregulated nucleolytic degradation by MRE11, creating DNA structures (which may not be DSEs) [94] that trigger chromosome aberrations [76]. In the absence of FANCD2, FAN1 could increase degradation of replication forks [74]. In the absence of BRCA2 (and also BRCA1) reversed RF are generated [94], possibly in a Rad51-dependent manner [84]. Reversed RF were proposed to be the substrate of dysregulated MRE11-driven nucleolytic degradation, triggered by PTIP [90]. Fragile and collapsed RF cannot be resolved by HDR. Chromosome aberrations [71] increase albeit they may be limited by FANCD2-dependent activation of A-EJ at DSE [69]. E) In the absence of both BRCA2 and FANCD2, RF are degraded by PTIP/MRE11 [90]. However, A-EJ is not activated in the absence of FANCD2 [69], chromosomal aberrations increase and cell death is also increased [71].

to degrade nascent DNA to promote RF re-start, thus protecting genome stability [74,92,99,100]. Also, the p53 exonuclease activity (p53 exo), which is strongly impaired by a point mutation in H115 [101], promotes nascent DNA degradation to facilitate template switching [102]. Hence, the exonucleolytic processing of RF aid DNA replication across DNA lesions, but such processing should be limited by FA proteins (BRCA1, BRCA2, FANCD2, RAD51) to avoid dyseregulated degradation of nascent DNA.

RF re-start depends on FANCD2, BRCA1, FANCJ, and the Bloom helicase [74,103,104]. To promote RF re-start, FANCD2 stimulates loading of MRE11, CtIP and FAN1 nucleases to RF but limits their nucleolytic activity [74,103,105]. Intriguingly, such events of RF re-start are independent of FANCI and FA core components [74]. The level of coordination between RF transactions that depend or not on FANCD2-monoubiquitylation is unknown. It has been proposed that monoubiquitylation ensures the localization of FANCD2 to RFs, whereas deubiquitylation of FANCD2 is required for fork protection [2]. Furthermore, DNA replication can also be regulated by FA components in a FANCD2-independent manner. For example, FANCI has a FANCD2-independent role in the Dbf4-dependent Cdc7 kinase (DDK)-dependent firing of dormant origins in conditions of mild replication stress [106]. Moreover, under such conditions of low replication stress (which are insufficient to cause checkpoint activation) FANCD2 counteracts FANCI–mediated origin firing [106]. Other components of the FA pathway including PALB2 (FANCN) and FANCJ were also implicated in events that aid DNA replication [104,107] in a manner that prevent RF breakage. Together, these results demonstrate that the FA pathway support multiple DNA replication transactions.

Please cite this article in press as: M.B. Federico, et al., Beyond interstrand crosslinks repair: contribution of FANCD2 and other Fanconi Anemia proteins to the replication of DNA, Mutat Res Fund Mol Mech Mutagen (2017), http://dx.doi.org/10.1016/j.mrfmmm.2017.09.004

The complex contribution of FANCD2 to DNA replication is also highlighted when analyzing the length of the nascent DNA track. The average length of those tracks depend on the combinatorial effect of a number of DNA replication transactions including permanent or transient stalling, RF reversal and nascent DNA degradation. In general, genotoxic agents cause a reduction in track length, presumably because of a temporal delay generated by DNA replication transactions at replication barriers (e.g. [74,84,92,94,95,105]), but exceptional lengthening has been also reported (e.g. [95]). Track length is both positively and negatively regulated by FANCD2. Two hours after HU treatment, FANCD2 depletion causes excessive elongation of the track length [108]. The RF transactions that prevent dysregulated elongation of nascent DNA involve a ubiquitin-independent interaction of FANCD2 with the CMG helicase [108] and the interaction of ubiquitylated FANCD2 with the FAN1 nuclease [98]. In contrast, at 5 h after HU treatment, nascent DNA tracks are shortened in the absence of FANCD2. Such reduction in nascent DNA tracks results from MRE11-dependent degradation of stalled forks in the absence of ubiquitylated FANCD2 [76] and on the nuclease activity of FAN1 [74]. In conclusion, not only HDR proteins but also FANCD2 attenuate DSE formation by protecting persistently stalled RFs and promoting their reactivation.

4.2. Biological relevance

Genomic instability strongly correlates with alterated DNA replication choreography in FANCD2-depleted samples. The main challenge has been to determine whether such genomic instability is the consequence of: a) DNA replication defects or b) DSE generated as a consequence of DNA replication deficiencies.

FANCD2-depletion increases the nucleolytic degradation of nascent DNA by MRE11 and FAN1 and the genomic instability of cells (Fig. 4C) [74,76]. However, the causal relationship between the dysregulation of nascent DNA degradation and the increase in the genomic instability of cells is unclear. In this respect, important information was gained in the context of BRCA2 depletion [90,94]. Depletion of the MLL3/4 complex protein, PTIP, inhibits the recruitment of the MRE11 nuclease to BRCA1/2-deficient stalled replication forks. In that way, PTIP restores the rate of nascent DNA synthesis, reducing the accumulation of chromosomic aberrations with no restoration of HDR at DSBs [90]. A direct association between impaired DNA replication and increased genomic instability has been established utilizing a BRCA2 mutant proficient for HDR but deficient in RF protection (BRCA2 S3291A). Such HDR proficient BRCA2 mutant was less efficient than wtBRCA2 in restoring the genomic stability of BRCA2 deficient cells treated with HU [94]. It was thereafter concluded that defective DNA replication can directly trigger gemonic instability. It is however puzzling to envisage how chromatidic aberrations, which were frequently associated with unleashed S-phase-associated NHEJ [24–26,28,56] accumulate in cells proficient for HDR. It has been proposed that the structure of unprotected RFs (reversed forks) may expose potential sites for aberrant interchromosomal end-joining (at the tip of the reversed fork) [94]. In addition, it has been showed that RFs derived from origins that fire after HU treatment are preferentially escorted by NHEJ factors rather than by HDR factors [109]. While it is possible that aberrant RF structures would be processable preferentially by NHEJ in HDR proficient environments, the specific conditions in which NHEJ can precede HDR during DSE resolution in S phase need further elucidation.

As mentioned in Section 4.1, the individual or combined depletion of FAN1 and FANCD2 exacerbate elongation of replication forks during the first two hours after HU treatment. A similar degree of epistasis was observed when documenting chromosomes abnormalties [98]. Micronuclei were also reported in FAN1-depleted conditions [74]. Remarkably, a FAN1 variant found in a patient with high-risk pancreatic cancers also causes genomic instability [98]. These results reinforce the relevance of RF protection by FANCD2 to the genomic stability of cells. However, whether the replication defect in FAN1-depleted cells cause genomic instability independently of DSE formation remains to be tested.

Finally, FANCD2 has been identified as a potential factor for promotion of resistance to PARP inhibitors in BRCA2-depleted cells [71]. Specifically, FANCD2 elimination slows down RF progression [69,71] and prevents the accumulation of chromatidic aberrations and cell death in BRCA2-depleted cells [71]. The protective effect of FANCD2 may not be linked to RF degradation as MRE11 activity would be already unleashed because of BRCA2 elimination. Remarkably, such protective effect is also independent from HDR as BRCA2-depleted cells are already deficient in HDR. The evidence suggest that such protection may involve a role of FANCD2 in the pathway choice downstream of DSEs formation. In fact, in the absence of BRCA1/2, FANCD2 promotes A-EJ (Fig. 4D) [69] (discussed in Section 3.2). As FANCD2-triggered A-EJ is associated with cell survival [69], these observations are very relevant because the generation of resistant tumors has been identified as a main reason for the failure of PARP treatment in the clinic [110]. While many aspects of the adaptation of RF to damaged DNA templates are still unknow, Fig. 4 illustrates the current, yet incomplete, knowledge on the effect that BRCA1, BRCA2, Rad51 and FANCD2 loss has on the replication of damaged DNA.

5. Contribution of FANCD2 and other FA proteins to the correct finalization of DNA replication

5.1. Mechanistic insights

Many DNA structures can block DNA replication (e.g. R-loops, G4 cuadruplexs, telomeres, centromeres). While a number of cellular responses such as origin firing and checkpoint signals may favor their replication during S phase [111,112], it is becoming evident that such mechanisms may not be failsafe. Thus, more frequently than once thought, cells may enter mitosis without completing S-phase. The DNA that is not synthesized during S phase may require mitotic DNA synthesis for its transmission to the next cell generations for its completion.

It has been proposed that DNA replication at hard-to-replicate regions such as common fragile sites (CFS) might be completed during M phase. In prophase, the nuclease Mus81 is recruited to CFSs, promoting POLD3-dependent DNA synthesis. In that way, chromosome mis-segregation is minimized [113]. The persistence of under-replicated DNA in early mitotic cells is manifested by the presence of ultra-fine DNA bridges (UFB) coated with RPA at CFS and at other problematic regions such as telomeres and centromeres [114–116]. Such DNA regions are also coated in their entire length by PLK1-interacting checkpoint helicase (PICH), which is an ATP-dependent DNA translocase [117–119]. The interaction of PICH with DNA increases as the DNA stretches [118]. PICH promotes bridge resolution at the end of anaphase by recruiting BTRR (BLM helicase/topoisomerase IIIa (TOPOIIIa)/RMI1 and RMI2 cofactors), a complex that resolves double Holliday complexes, to the UFBs [120]. If not resolved, UFBs can lead to chromosome breakage and other chromosome lesions that are transmitted to daughter cells and are visible as nuclear compartments shielded with p53-binding protein 1 (53BP1) in the subsequent G1 [121].

It has been long known that FANCD2 and FANCA are required to maintain the stability of chromosomal fragile sites [75]. More recently, FANCD2 and FANCI were shown to localize to the most frequently expressed fragile sites, FRA3B and FRA16D, colocalizing with BLM [115,122]. In UFBs, FANCD2 colocalizes with structure-specific endonucleases XPF and MUS81, which, together with BLM promote the accurate processing of under-replicated DNA that per-

Please cite this article in press as: M.B. Federico, et al., Beyond interstrand crosslinks repair: contribution of FANCD2 and other Fanconi Anemia proteins to the replication of DNA, Mutat Res Fund Mol Mech Mutagen (2017), http://dx.doi.org/10.1016/j.mrfmmm.2017.09.004

sist at CFSs until mitosis [123]. Intriguingly, FANCD2 localizes to the UFB 'termini' only [122]. Such specific localization may contribute to the stabilization of the UFBs, and/or to the recruitment of PICH onto each type of UFB [116]. FANCM is also recruited to UFBs, at a stage in which BLM and PICH are no longer recruited to UFBs [115,124]. It is possible that the PICH and BTRR complexes resolve some UFBs, while other complexes resolve persistent UFBs in telophase [116].

FANCD2 specifically associates with CFS loci irrespective of whether the chromosome is broken [115], which may suggest that it functions beyond UFB protection. In fact, a recent report has demonstrated that FANCD2 not only protects under-replicated CFS but promotes their bidirectional DNA replication, favoring the finalization of CFS duplication [125]. When FANCD2 is depleted, R loops accumulate in CFS loci promoting replication pausing and triggering the firing of dormant origins. Intriguingly, such function of FANCD2 is independent of the FA core complex. In conclusion, FANCD2 function is crucial for CFS duplication and segregation [125]. FANCD2 and other FA proteins may also control mitosis in a DNA replication-independent manner as these proteins localize to the mitotic apparatus. Remarkably, depletion of FA proteins was shown to dysregulate the spindle assembly checkpoint [126]. Taking together the current knowledge, it is clear that FA proteins protects many aspects of DNA replication and chromosome segregation. More work is required to identify the extent to which the dirsruption of each of these functions contributes to the chromosomal instability of patients with FA.

5.2. Biological relevance

CFS are hotspots for genome instability both in cancers and neurological syndromes [127]. The most characterized CFS are FRA3B and FRA16D, which encode the putative tumor-suppressor genes FHIT and WWOX, respectively [128]. Moreover, as CFS loci can harbor long transcribed genes, R loops may trigger genomic instability preferentially at those sites [128]. In fact, FA proteins protect cells from the accumulation of DNA:RNA hybrids [77,129]. However, given the current inability to functionally dissect the many functions of FANCD2 in S phase and beyond, the specific contribution of UFB regulation and CFS protection to the genomic stability of FANCD2-depleted cells is unknown. Notwithstanding this, the relevance of successful CFS duplication for the genomic stability of cells is highlighted by a number of evidences. For example, UFB and the accumulation of DNA damage in the following G1 phase, increase after depletion of endonucleases that process UFBs [123]. The need of FANCD2 for replication of CFS is evident in lymphoblasts but not in cells that are rich in initiation events such as fibroblasts [125]. Also, POLD3-dependent mitotic DNA synthesis is enhanced in aneuploid cancer cells that exhibit intrinsically high levels of chromosomal instability (CIN+) [113]. These findings indicate that replication stress enhances the reliance of tumor cells on FA proteins. Such observations may suggest that FA proteins-driven mitotic transactions could represent a target for cancer treatment.

6. Concluding remarks

During the last 15 years a solid body of evidence has demonstrated that FANCD2 and other FA proteins are key regulators of multiple DNA replication-associated transactions that include but are not limited to ICL repair. A number of new functions were described for FA proteins and their relative contribution to the genomic stability of cells is currently under identification. Acquiring mechanistic insights into such unanticipated functions of the FA pathway may provide crucial understanding of the aetiology of carcinogenesis in FA patients. The identification of separation of function mutants of different components of the FA pathway may be key to reveal the biological relevance of different activities within a same protein. For example, cells expressing a Rad51 T131P, which has been identified in a FA-like patient, are HDR proficient but fail to correctly repair ICLs, hence suggesting not overlapping functions of Rad51 at RFs and DSE repair [130]. Separation of function mutants such as Rad51 T131P may help to answer important open questions which include but are not limited to the following:

1. How important is the FA pathway for the facilitation of DNA replication across cell-intrinsic obstacles? Not only FANCD2 is important for CFS replication (Section 5.1) but also, other line of evidence link DNA replication across G4s and R-loops with the FA pathway [77,129].
2. Does FANCD2 participate in the DSE pathway choice after every genotoxic challenge? What about other FA proteins? How central is FANCD2-directed processing of DSE for the genomic stability of cells?
3. Is the pathological nascent DNA degradation observed after FANCD2, BRCA2, BRCA1 depletion sustained only after HU/APH or can it be observed after other types of genotoxins? Does MRE11 degrades nascent DNA on the DNA structures after Rad51 depletion? And after all genotoxic challenges?
4. How is the FA pathway turned off? Such mechanism may involve the deubiquitylating enzyme USP1, which removes the ubiquitin from FANCD2 [131,132]. Intriguingly, USP1 depletion increases sensitivity to crosslinking agents, despite the elevated levels of ubiquitylated FANCD2 [133,134]. Which are the molecular bases of such sensitivity? Are results similar after genotoxins that do not cause ICL accumulation?.
5. Does the FA pathway contribute in similar ways to unperturbed, mild or acute replication stress? FANCD2 was reported to promote origin firing during unperturbed replication [135] but to inhibit it after mild replication stress [106]. Hence, the potential interaction of FA with other cellular pathways may need further exploration.
6. Do FA proteins participate in other mechanisms of DNA repair other than ICL repair? What is the contribution of FA proteins to DNA damage tolerance pathways? BRCA1 was reported to promote Nucleotide Excision Repair (NER) in S-phase [136]. Also, NER is promoted by FANCJ in a process that requires mistmatch repair proteins [137]. TLS is regulated by BRCA1 and some FA core components [136,138]. Hence, the degree of interaction between the FA pathway with other DNA damage response pathways should be further explored.

Acknowledgements

We would like to thank Marina Gonzalez Besteiro, Lucas Pontel and Graciela Spivak for helpful comments and critical reading of the manuscript. Work in V. Gottifrediís laboratory is funded by PICT grants from Agencia Nacional de Promoción Científica y Tecnológica (ANPCyT) and from the Argentinian National Cancer Institute (NCI). MBF and NP are supported by fellowships from the National Council of Scientific and Technological Research (CONICET) in Argentina. PC is supported by a fellowship of ANPCyT[v1] and Vanesa Gottifredi is a researcher from CONICET. We apologize to authors whose work could not be cited due to space restrictions. The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.mrfmmm.2017.09.004.

References

[1] B.M. Auerbach, A.D. Joenje, H. Fanconi, in: M.-H. Medical (Ed.), Anemia in Metabolic and Molecular Bases of Inherited Disease, 2001–2017, pp. 753–768, New York.
[2] R. Ceccaldi, P. Sarangi, A.D. D'Andrea, The Fanconi anaemia pathway: new players and new functions, Nat. Rev. Mol. Cell Biol. 17 (2016) 337–349.
[3] M.C. Kottemann, A. Smogorzewska, Fanconi anaemia and the repair of Watson and Crick DNA crosslinks, Nature 493 (2013) 356–363.
[4] M. Landau, B.R. Krafchik, The diagnostic value of cafe-au-lait macules, J. Am. Acad. Dermatol. 40 (1999) 877–890, quiz 891-872.
[5] L.E. Romick-Rosendale, V.W. Lui, J.R. Grandis, S.I. Wells, The Fanconi anemia pathway: repairing the link between DNA damage and squamous cell carcinoma, Mutat. Res. 743–744 (2013) 78–88.
[6] P.S. Rosenberg, M.H. Greene, B.P. Alter, Cancer incidence in persons with Fanconi anemia, Blood 101 (2003) 822–826.
[7] A.D. Auerbach, S.R. Wolman, Susceptibility of Fanconi's anaemia fibroblasts to chromosome damage by carcinogens, Nature 261 (1976) 494–496.
[8] M.S. Sasaki, A. Tonomura, A high susceptibility of Fanconi's anemia to chromosome breakage by DNA cross-linking agents, Cancer Res. 33 (1973) 1829–1836.
[9] Fanconi Anemia Research Fund. http://fanconi.org/.
[10] M.A. Whitney, H. Saito, P.M. Jakobs, R.A. Gibson, R.E. Moses, M. Grompe, A common mutation in the FACC gene causes Fanconi anaemia in Ashkenazi Jews, Nat. Genet. 4 (1993) 202–205.
[11] D. Bluteau, J. Masliah-Planchon, C. Clairmont, A. Rousseau, R. Ceccaldi, C. Dubois d'Enghien, O. Bluteau, W. Cuccuini, S. Gachet, R. Peffault de Latour, T. Leblanc, G. Socie, A. Baruchel, D. Stoppa-Lyonnet, A.D. D'Andrea, J. Soulier, Biallelic inactivation of REV7 is associated with Fanconi anemia, J. Clin. Invest. 126 (2016) 3580–3584.
[12] N.E. Mamrak, A. Shimamura, N.G. Howlett, Recent discoveries in the molecular pathogenesis of the inherited bone marrow failure syndrome Fanconi anemia, Blood Rev. 31 (2017) 93–99.
[13] K. Knies, S. Inano, M.J. Ramirez, M. Ishiai, J. Surralles, M. Takata, D. Schindler, Biallelic mutations in the ubiquitin ligase RFWD3 cause Fanconi anemia, J. Clin. Invest. 127 (2017) 3013–3027.
[14] B.P. Alter, Fanconi's anemia and malignancies, Am. J. Hematol. 53 (1996) 99–110.
[15] H. Joenje, K.J. Patel, The emerging genetic and molecular basis of Fanconi anaemia, Nat. Rev. Genet. 2 (2001) 446–457.
[16] M. Bogliolo, J. Surralles, Fanconi anemia: a model disease for studies on human genetics and advanced therapeutics, Curr. Opin. Genet. Dev. 33 (2015) 32–40.
[17] A.T. Wang, A. Smogorzewska, SnapShot: Fanconi anemia and associated proteins, Cell 160 (2015), 354-354 e351.
[18] S.M. Domchek, J. Tang, J. Stopfer, D.R. Lilli, N. Hamel, M. Tischkowitz, A.N. Monteiro, T.E. Messick, J. Powers, A. Yonker, F.J. Couch, D.E. Goldgar, H.R. Davidson, K.L. Nathanson, W.D. Foulkes, R.A. Greenberg, Biallelic deleterious BRCA1 mutations in a woman with early-onset ovarian cancer, Cancer Discov. 3 (2013) 399–405.
[19] S.L. Sawyer, L. Tian, M. Kahkonen, J. Schwartzentruber, M. Kircher, J. Majewski, D.A. Dyment, A.M. Innes, K.M. Boycott, L.A. Moreau, J.S. Moilanen, R.A. Greenberg, Biallelic mutations in BRCA1 cause a new Fanconi anemia subtype, Cancer Discov. 5 (2015) 135–142.
[20] T.R. Singh, S.T. Bakker, S. Agarwal, M. Jansen, E. Grassman, B.C. Godthelp, A.M. Ali, C.H. Du, M.A. Rooimans, Q. Fan, K. Wahengbam, J. Steltenpool, P.R. Andreassen, D.A. Williams, H. Joenje, J.P. de Winter, A.R. Meetei, Impaired FANCD2 monoubiquitination and hypersensitivity to camptothecin uniquely characterize Fanconi anemia complementation group M, Blood 114 (2009) 174–180.
[21] J. Michl, J. Zimmer, M. Tarsounas, Interplay between Fanconi anemia and homologous recombination pathways in genome integrity, EMBO J. 35 (2016) 909–923.
[22] M.J. Jones, T.T. Huang, The Fanconi anemia pathway in replication stress and DNA crosslink repair, Cell. Mol. Life Sci.: CMLS 69 (2012) 3963–3974.
[23] J. Zhang, J.C. Walter, Mechanism and regulation of incisions during DNA interstrand cross-link repair, DNA Repair 19 (2014) 135–142.
[24] A. Adamo, S.J. Collis, C.A. Adelman, N. Silva, Z. Horejsi, J.D. Ward, E. Martinez-Perez, S.J. Boulton, A. La Volpe, Preventing nonhomologous end joining suppresses DNA repair defects of Fanconi anemia, Mol. Cell 39 (2010) 25–35.
[25] S.F. Bunting, E. Callen, M.L. Kozak, J.M. Kim, N. Wong, A.J. Lopez-Contreras, T. Ludwig, R. Baer, R.B. Faryabi, A. Malhowski, H.T. Chen, O. Fernandez-Capetillo, A. D'Andrea, A. Nussenzweig, BRCA1 functions independently of homologous recombination in DNA interstrand crosslink repair, Mol. Cell 46 (2012) 125–135.
[26] S.F. Bunting, E. Callen, N. Wong, H.T. Chen, F. Polato, A. Gunn, A. Bothmer, N. Feldhahn, O. Fernandez-Capetillo, L. Cao, X. Xu, C.X. Deng, T. Finkel, M. Nussenzweig, J.M. Stark, A. Nussenzweig, 53BP1 inhibits homologous recombination in Brca1-deficient cells by blocking resection of DNA breaks, Cell 141 (2010) 243–254.
[27] S. Houghtaling, C. Timmers, M. Noll, M.J. Finegold, S.N. Jones, M.S. Meyn, M. Grompe, Epithelial cancer in Fanconi anemia complementation group D2 (Fancd2) knockout mice, Genes. Dev. 17 (2003) 2021–2035.
[28] P. Pace, G. Mosedale, M.R. Hodskinson, I.V. Rosado, M. Sivasubramaniam, K.J. Patel, Ku70 corrupts DNA repair in the absence of the Fanconi anemia pathway, Science 329 (2010) 219–223.
[29] C.A. Waters, N.T. Strande, D.W. Wyatt, J.M. Pryor, D.A. Ramsden, Nonhomologous end joining: a good solution for bad ends, DNA Repair 17 (2014) 39–51.
[30] J.I. Garaycoechea, K.J. Patel, Why does the bone marrow fail in Fanconi anemia? Blood 123 (2014) 26–34.
[31] R. Ceccaldi, K. Parmar, E. Mouly, M. Delord, J.M. Kim, M. Regairaz, M. Pla, N. Vasquez, Q.S. Zhang, C. Pondarre, R. Peffault de Latour, E. Gluckman, M. Cavazzana-Calvo, T. Leblanc, J. Larghero, M. Grompe, G. Socie, A.D. D'Andrea, J. Soulier, Bone marrow failure in Fanconi anemia is triggered by an exacerbated p53/p21 DNA damage response that impairs hematopoietic stem and progenitor cells, Cell Stem Cell 11 (2012) 36–49.
[32] D. Walter, A. Lier, A. Geiselhart, F.B. Thalheimer, S. Huntscha, M.C. Sobotta, B. Moehrle, D. Brocks, I. Bayindir, P. Kaschutnig, K. Muedder, C. Klein, A. Jauch, T. Schroeder, H. Geiger, T.P. Dick, T. Holland-Letz, P. Schmezer, S.W. Lane, M.A. Rieger, M.A. Essers, D.A. Williams, A. Trumpp, M.D. Milsom, Exit from dormancy provokes DNA-damage-induced attrition in haematopoietic stem cells, Nature 520 (2015) 549–552.
[33] C. Marietta, L.H. Thompson, J.E. Lamerdin, P.J. Brooks, Acetaldehyde stimulates FANCD2 monoubiquitination, H2AX phosphorylation, and BRCA1 phosphorylation in human cells in vitro: implications for alcohol-related carcinogenesis, Mutat. Res. 664 (2009) 77–83.
[34] F. Langevin, G.P. Crossan, I.V. Rosado, M.J. Arends, K.J. Patel, Fancd2 counteracts the toxic effects of naturally produced aldehydes in mice, Nature 475 (2011) 53–58.
[35] M. Mechilli, A. Schinoppi, K. Kobos, A.T. Natarajan, F. Palitti, DNA repair deficiency and acetaldehyde-induced chromosomal alterations in CHO cells, Mutagenesis 23 (2008) 51–56.
[36] J.R. Ridpath, A. Nakamura, K. Tano, A.M. Luke, E. Sonoda, H. Arakawa, J.M. Buerstedde, D.A. Gillespie, J.E. Sale, M. Yamazoe, D.K. Bishop, M. Takata, S. Takeda, M. Watanabe, J.A. Swenberg, J. Nakamura, Cells deficient in the FANC/BRCA pathway are hypersensitive to plasma levels of formaldehyde, Cancer Res. 67 (2007) 11117–11122.
[37] I.V. Rosado, F. Langevin, G.P. Crossan, M. Takata, K.J. Patel, Formaldehyde catabolism is essential in cells deficient for the Fanconi anemia DNA-repair pathway, Nat. Struct. Mol. Biol. 18 (2011) 1432–1434.
[38] J.I. Garaycoechea, G.P. Crossan, F. Langevin, M. Daly, M.J. Arends, K.J. Patel, Genotoxic consequences of endogenous aldehydes on mouse haematopoietic stem cell function, Nature 489 (2012) 571–575.
[39] L.B. Pontel, I.V. Rosado, G. Burgos-Barragan, J.I. Garaycoechea, R. Yu, M.J. Arends, G. Chandrasekaran, V. Broecker, W. Wei, L. Liu, J.A. Swenberg, G.P. Crossan, K.J. Patel, Endogenous formaldehyde is a hematopoietic stem cell genotoxin and metabolic carcinogen, Mol. Cell 60 (2015) 177–188.
[40] G. Pagano, P. Degan, M. d'Ischia, F.J. Kelly, B. Nobili, F.V. Pallardo, H. Youssoufian, A. Zatterale, Oxidative stress as a multiple effector in Fanconi anaemia clinical phenotype, Eur. J. Haematol. 75 (2005) 93–100.
[41] Q. Pang, P.R. Andreassen, Fanconi anemia proteins and endogenous stresses, Mutat. Res. 668 (2009) 42–53.
[42] T. Aparicio, R. Baer, J. Gautier, DNA double-strand break repair pathway choice and cancer, DNA Repair 19 (2014) 169–175.
[43] E. Petermann, M.L. Orta, N. Issaeva, N. Schultz, T. Helleday, Hydroxyurea-stalled replication forks become progressively inactivated and require two different RAD51-mediated pathways for restart and repair, Mol. Cell 37 (2010) 492–502.
[44] A. Pepe, S.C. West, MUS81-EME2 promotes replication fork restart, Cell Rep. 7 (2014) 1048–1055.
[45] H. Techer, S. Koundrioukoff, S. Carignon, T. Wilhelm, G.A. Millot, B.S. Lopez, O. Brison, M. Debatisse, Signaling from Mus81-Eme2-dependent DNA damage elicited by chk1 deficiency modulates replication fork speed and origin usage, Cell Rep. 14 (2016) 1114–1127.
[46] Y. Hashimoto, F. Puddu, V. Costanzo, RAD51- and MRE11-dependent reassembly of uncoupled CMG helicase complex at collapsed replication forks, Nat. Struct. Mol. Biol. 19 (2011) 17–24.
[47] T. Taniguchi, I. Garcia-Higuera, B. Xu, P.R. Andreassen, R.C. Gregory, S.T. Kim, W.S. Lane, M.B. Kastan, A.D. D'Andrea, Convergence of the fanconi anemia and ataxia telangiectasia signaling pathways, Cell 109 (2002) 459–472.
[48] S.J. Collis, L.J. Barber, J.D. Ward, J.S. Martin, S.J. Boulton, C. elegans FANCD2 responds to replication stress and functions in interstrand cross-link repair, DNA Repair 5 (2006) 1398–1406.
[49] C.S. Djuzenova, M. Flentje, Characterization of Fanconi anemia fibroblasts in terms of clonogenic survival and DNA damage assessed by the Comet assay, Med. Sci. Monit.: Int. Med. J. Exp. Clin. Res. 8 (2002) BR421–430.
[50] J.M. Hinz, N.A. Yamada, E.P. Salazar, R.S. Tebbs, L.H. Thompson, Influence of double-strand-break repair pathways on radiosensitivity throughout the cell cycle in CHO cells, DNA Repair 4 (2005) 782–792.
[51] S. Houghtaling, A. Newell, Y. Akkari, T. Taniguchi, S. Olson, M. Grompe, Fancd2 functions in a double strand break repair pathway that is distinct from non-homologous end joining, Hum. Mol. Genet. 14 (2005) 3027–3033.
[52] K. Nakanishi, Y.G. Yang, A.J. Pierce, T. Taniguchi, M. Digweed, A.D. D'Andrea, Z.Q. Wang, M. Jasin, Human Fanconi anemia monoubiquitination pathway promotes homologous DNA repair, Proc. Natl. Acad. Sci. U. S. A. 102 (2005) 1110–1115.
[53] K. Nakanishi, F. Cavallo, L. Perrouault, C. Giovannangeli, M.E. Moynahan, M. Barchi, E. Brunet, M. Jasin, Homology-directed Fanconi anemia pathway

Please cite this article in press as: M.B. Federico, et al., Beyond interstrand crosslinks repair: contribution of FANCD2 and other Fanconi Anemia proteins to the replication of DNA, Mutat Res Fund Mol Mech Mutagen (2017), http://dx.doi.org/10.1016/j.mrfmmm.2017.09.004

cross-link repair is dependent on DNA replication, Nat. Struct. Mol. Biol. 18 (2011) 500–503.
[54] K. Hanada, M. Budzowska, S.L. Davies, E. van Drunen, H. Onizawa, H.B. Beverloo, A. Maas, J. Essers, I.D. Hickson, R. Kanaar, The structure-specific endonuclease Mus81 contributes to replication restart by generating double-strand DNA breaks, Nat. Struct. Mol. Biol. 14 (2007) 1096–1104.
[55] M. Li, F. Cole, D.S. Patel, S.M. Misenko, J. Her, A. Malhowski, A. Alhamza, H. Zheng, R. Baer, T. Ludwig, M. Jasin, A. Nussenzweig, L. Serrano, S.F. Bunting, 53BP1 ablation rescues genomic instability in mice expressing 'RING-less' BRCA1, EMBO Rep. 17 (2016) 1532–1541.
[56] M.B. Federico, M.B. Vallerga, A. Radl, N.S. Paviolo, J.L. Bocco, M. Di Giorgio, G. Soria, V. Gottifredi, Chromosomal integrity after UV irradiation requires FANCD2-mediated repair of double strand breaks, PLoS Genet. 12 (2016) e1005792.
[57] J. Dunn, M. Potter, A. Rees, T.M. Runger, Activation of the Fanconi anemia/BRCA pathway and recombination repair in the cellular response to solar ultraviolet light, Cancer Res. 66 (2006) 11140–11147.
[58] B.C. Godthelp, P.P. van Buul, N.G. Jaspers, E. Elghalbzouri-Maghrani, A. van Duijn-Goedhart, F. Arwert, H. Joenje, M.Z. Zdzienicka, Cellular characterization of cells from the Fanconi anemia complementation group, FA-D1/BRCA2, Mutat. Res. 601 (2006) 191–201.
[59] S. Hirano, K. Yamamoto, M. Ishiai, M. Yamazoe, M. Seki, N. Matsushita, M. Ohzeki, Y.M. Yamashita, H. Arakawa, J.M. Buerstedde, T. Enomoto, S. Takeda, L.H. Thompson, M. Takata, Functional relationships of FANCC to homologous recombination, translesion synthesis, and BLM, EMBO J. 24 (2005) 418–427.
[60] I.R. Kelsall, J. Langenick, C. MacKay, K.J. Patel, A.F. Alpi, The Fanconi anaemia components UBE2T and FANCM are functionally linked to nucleotide excision repair, PLoS One 7 (2012) e36970.
[61] Q. Liang, T.S. Dexheimer, P. Zhang, A.S. Rosenthal, M.A. Villamil, C. You, Q. Zhang, J. Chen, C.A. Ott, H. Sun, D.K. Luci, B. Yuan, A. Simeonov, A. Jadhav, H. Xiao, Y. Wang, D.J. Maloney, Z. Zhuang, A selective USP1-UAF1 inhibitor links deubiquitination to DNA damage responses, Nat. Chem. Biol. 10 (2014) 298–304.
[62] E. Renaud, F. Rosselli, FANC pathway promotes UV-induced stalled replication forks recovery by acting both upstream and downstream Poleta and Rev1, PLoS One 8 (2013) e53693.
[63] J. Xie, R. Litman, S. Wang, M. Peng, S. Guillemette, T. Rooney, S.B. Cantor, Targeting the FANCJ-BRCA1 interaction promotes a switch from recombination to poleta-dependent bypass, Oncogene 29 (2010) 2499–2508.
[64] K. Yamamoto, S. Hirano, M. Ishiai, K. Morishima, H. Kitao, K. Namikoshi, M. Kimura, N. Matsushita, H. Arakawa, J.M. Buerstedde, K. Komatsu, L.H. Thompson, M. Takata, Fanconi anemia protein FANCD2 promotes immunoglobulin gene conversion and DNA repair through a mechanism related to homologous recombination, Mol. Cell. Biol. 25 (2005) 34–43.
[65] A.P. Bertolin, S.F. Mansilla, V. Gottifredi, The identification of translesion DNA synthesis regulators: inhibitors in the spotlight, DNA Repair 32 (2015) 158–164.
[66] B. Eppink, A.A. Tafel, K. Hanada, E. van Drunen, I.D. Hickson, J. Essers, R. Kanaar, The response of mammalian cells to UV-light reveals Rad54-dependent and independent pathways of homologous recombination, DNA Repair 10 (2011) 1095–1105.
[67] G.A. Garinis, J.R. Mitchell, M.J. Moorhouse, K. Hanada, H. de Waard, D. Vandeputte, J. Jans, K. Brand, M. Smid, P.J. van der Spek, J.H. Hoeijmakers, R. Kanaar, G.T. van der Horst, Transcriptome analysis reveals cyclobutane pyrimidine dimers as a major source of UV-induced DNA breaks, EMBO J. 24 (2005) 3952–3962.
[68] H. Yajima, K.J. Lee, S. Zhang, J. Kobayashi, B.P. Chen, DNA double-strand break formation upon UV-induced replication stress activates ATM and DNA-PKcs kinases, J. Mol. Biol. 385 (2009) 800–810.
[69] Z. Kais, B. Rondinelli, A. Holmes, C. O'Leary, D. Kozono, A.D. D'Andrea, R. Ceccaldi, FANCD2 maintains fork stability in BRCA1/2-deficient tumors and promotes alternative end-joining DNA repair, Cell Rep. 15 (2016) 2488–2499.
[70] R. Ceccaldi, J.C. Liu, R. Amunugama, I. Hajdu, B. Primack, M.I. Petalcorin, K.W. O'Connor, P.A. Konstantinopoulos, S.J. Elledge, S.J. Boulton, T. Yusufzai, A.D. D'Andrea, Homologous-recombination-deficient tumours are dependent on Poltheta-mediated repair, Nature 518 (2015) 258–262.
[71] J. Michl, J. Zimmer, F.M. Buffa, U. McDermott, M. Tarsounas, FANCD2 limits replication stress and genome instability in cells lacking BRCA2, Nat. Struct. Mol. Biol. 23 (2016) 755–757.
[72] A.M. Kolinjivadi, V. Sannino, A. de Antoni, H. Techer, G. Baldi, V. Costanzo, Moonlighting at replication forks – a new life for homologous recombination proteins BRCA1, BRCA2 and RAD51, FEBS Lett. 591 (2017) 1083–1100.
[73] N. Spardy, A. Duensing, D. Charles, N. Haines, T. Nakahara, P.F. Lambert, S. Duensing, The human papillomavirus type 16 E7 oncoprotein activates the Fanconi anemia (FA) pathway and causes accelerated chromosomal instability in FA cells, J. Virol. 81 (2007) 13265–13270.
[74] I. Chaudhury, D.R. Stroik, A. Sobeck, FANCD2-controlled chromatin access of the Fanconi-associated nuclease FAN1 is crucial for the recovery of stalled replication forks, Mol. Cell. Biol. 34 (2014) 3939–3954.
[75] N.G. Howlett, T. Taniguchi, S.G. Durkin, A.D. D'Andrea, T.W. Glover, The Fanconi anemia pathway is required for the DNA replication stress response and for the regulation of common fragile site stability, Hum. Mol. Genet. 14 (2005) 693–701.
[76] K. Schlacher, H. Wu, M. Jasin, A distinct replication fork protection pathway connects Fanconi anemia tumor suppressors to RAD51-BRCA1/2, Cancer Cell 22 (2012) 106–116.
[77] M.L. Garcia-Rubio, C. Perez-Calero, S.I. Barroso, E. Tumini, E. Herrera-Moyano, I.V. Rosado, A. Aguilera, The Fanconi Anemia pathway protects genome integrity from R-loops, PLoS Genet. 11 (2015) e1005674.
[78] Y. Wang, G. Ghosh, E.A. Hendrickson, Ku86 represses lethal telomere deletion events in human somatic cells, Proc. Natl. Acad. Sci. U. S. A. 106 (2009) 12430–12435.
[79] L. Costantino, S.K. Sotiriou, J.K. Rantala, S. Magin, E. Mladenov, T. Helleday, J.E. Haber, G. Iliakis, O.P. Kallioniemi, T.D. Halazonetis, Break-induced replication repair of damaged forks induces genomic duplications in human cells, Science 343 (2014) 88–91.
[80] S. Nik-Zainal, L.B. Alexandrov, D.C. Wedge, P. Van Loo, C.D. Greenman, K. Raine, D. Jones, J. Hinton, J. Marshall, L.A. Stebbings, A. Menzies, S. Martin, K. Leung, L. Chen, C. Leroy, M. Ramakrishna, R. Rance, K.W. Lau, L.J. Mudie, I. Varela, D.J. McBride, G.R. Bignell, S.L. Cooke, A. Shlien, J. Gamble, I. Whitmore, M. Maddison, P.S. Tarpey, H.R. Davies, E. Papaemmanuil, P.J. Stephens, S. McLaren, A.P. Butler, J.W. Teague, G. Jonsson, J.E. Garber, D. Silver, P. Miron, A. Fatima, S. Boyault, A. Langerod, A. Tutt, J.W. Martens, S.A. Aparicio, A. Borg, A.V. Salomon, G. Thomas, A.L. Borresen-Dale, A.L. Richardson, M.S. Neuberger, P.A. Futreal, P.J. Campbell, M.R. Stratton, Mutational processes molding the genomes of 21 breast cancers, Cell 149 (2012) 979–993.
[81] J. Zamborszky, B. Szikriszt, J.Z. Gervai, O. Pipek, A. Poti, M. Krzystanek, D. Ribli, J.M. Szalai-Gindl, I. Csabai, Z. Szallasi, C. Swanton, A.L. Richardson, D. Szuts, Loss of BRCA1 or BRCA2 markedly increases the rate of base substitution mutagenesis and has distinct effects on genomic deletions, Oncogene 36 (2017) 746–755.
[82] H. Ghezraoui, M. Piganeau, B. Renouf, J.B. Renaud, A. Sallmyr, B. Ruis, S. Oh, A.E. Tomkinson, E.A. Hendrickson, C. Giovannangeli, M. Jasin, E. Brunet, Chromosomal translocations in human cells are generated by canonical nonhomologous end-joining, Mol. Cell 55 (2014) 829–842.
[83] A.M. Carr, S. Lambert, Replication stress-induced genome instability: the dark side of replication maintenance by homologous recombination, J. Mol. Biol. 425 (2013) 4733–4744.
[84] R. Zellweger, D. Dalcher, K. Mutreja, M. Berti, J.A. Schmid, R. Herrador, A. Vindigni, M. Lopes, Rad51-mediated replication fork reversal is a global response to genotoxic treatments in human cells, J. Cell Biol. 208 (2015) 563–579.
[85] Y. Hashimoto, A. Ray Chaudhuri, M. Lopes, V. Costanzo, Rad51 protects nascent DNA from Mre11-dependent degradation and promotes continuous DNA synthesis, Nat. Struct. Mol. Biol. 17 (2010) 1305–1311.
[86] M. Lopes, M. Foiani, J.M. Sogo, Multiple mechanisms control chromosome integrity after replication fork uncoupling and restart at irreparable UV lesions, Mol. Cell 21 (2006) 15–27.
[87] K.J. Neelsen, M. Lopes, Replication fork reversal in eukaryotes: from dead end to dynamic response, Nat. Rev. Mol. Cell Biol. 16 (2015) 207–220.
[88] M. Berti, A. Ray Chaudhuri, S. Thangavel, S. Gomathinayagam, S. Kenig, M. Vujanovic, F. Odreman, T. Glatter, S. Graziano, R. Mendoza-Maldonado, F. Marino, B. Lucic, V. Biasin, M. Gstaiger, R. Aebersold, J.M. Sidorova, R.J. Monnat Jr., M. Lopes, A. Vindigni, Human RECQ1 promotes restart of replication forks reversed by DNA topoisomerase I inhibition, Nat. Struct. Mol. Biol. 20 (2013) 347–354.
[89] K. Fugger, M. Mistrik, K.J. Neelsen, Q. Yao, R. Zellweger, A.N. Kousholt, P. Haahr, W.K. Chu, J. Bartek, M. Lopes, I.D. Hickson, C.S. Sørensen, FBH1 catalyzes regression of stalled replication forks, Cell Rep. 10 (March) (2015), http://dx.doi.org/10.1016/j.celrep.2015.02.028, pii: S2211-1247(15)00174-6.
[90] A. Ray Chaudhuri, E. Callen, X. Ding, E. Gogola, A.A. Duarte, J.E. Lee, N. Wong, V. Lafarga, J.A. Calvo, N.J. Panzarino, S. John, A. Day, A.V. Crespo, B. Shen, L.M. Starnes, J.R. de Ruiter, J.A. Daniel, P.A. Konstantinopoulos, D. Cortez, S.B. Cantor, O. Fernandez-Capetillo, K. Ge, J. Jonkers, S. Rottenberg, S.K. Sharan, A. Nussenzweig, Replication fork stability confers chemoresistance in BRCA-deficient cells, Nature 535 (2016) 382–387.
[91] A. Ray Chaudhuri, Y. Hashimoto, R. Herrador, K.J. Neelsen, D. Fachinetti, R. Bermejo, A. Cocito, V. Costanzo, M. Lopes, Topoisomerase I poisoning results in PARP-mediated replication fork reversal, Nat. Struct. Mol. Biol. 19 (2012) 417–423.
[92] S. Thangavel, M. Berti, M. Levikova, C. Pinto, S. Gomathinayagam, M. Vujanovic, R. Zellweger, H. Moore, E.H. Lee, E.A. Hendrickson, P. Cejka, S. Stewart, M. Lopes, A. Vindigni, DNA2 drives processing and restart of reversed replication forks in human cells, J. Cell Biol. 208 (2015) 545–562.
[93] K.J. Neelsen, I.M. Zanini, S. Mijic, R. Herrador, R. Zellweger, A. Ray Chaudhuri, K.D. Creavin, J.J. Blow, M. Lopes, Deregulated origin licensing leads to chromosomal breaks by rereplication of a gapped DNA template, Genes. Dev. 27 (2013) 2537–2542.
[94] K. Schlacher, N. Christ, N. Siaud, A. Egashira, H. Wu, M. Jasin, Double-strand break repair-independent role for BRCA2 in blocking stalled replication fork degradation by MRE11, Cell 145 (2011) 529–542.
[95] M.B. Vallerga, S.F. Mansilla, M.B. Federico, A.P. Bertolin, V. Gottifredi, Rad51 recombinase prevents Mre11 nuclease-dependent degradation and excessive PrimPol-mediated elongation of nascent DNA after UV irradiation, Proc. Natl. Acad. Sci. U. S. A. 112 (2015) E6624–6633.
[96] S. Pathania, S. Bade, M. Le Guillou, K. Burke, R. Reed, C. Bowman-Colin, Y. Su, D.T. Ting, K. Polyak, A.L. Richardson, J. Feunteun, J.E. Garber, D.M. Livingston,

Please cite this article in press as: M.B. Federico, et al., Beyond interstrand crosslinks repair: contribution of FANCD2 and other Fanconi Anemia proteins to the replication of DNA, Mutat Res Fund Mol Mech Mutagen (2017), http://dx.doi.org/10.1016/j.mrfmmm.2017.09.004

BRCA1 haploinsufficiency for replication stress suppression in primary cells, Nat. Commun. 5 (2014) 5496.
[97] S. Ying, F.C. Hamdy, T. Helleday, Mre11-dependent degradation of stalled DNA replication forks is prevented by BRCA2 and PARP1, Cancer Res. 72 (2012) 2814–2821.
[98] C. Lachaud, A. Moreno, F. Marchesi, R. Toth, J.J. Blow, J. Rouse, Ubiquitinated Fancd2 recruits Fan1 to stalled replication forks to prevent genome instability, Science 351 (2016) 846–849.
[99] J.P. Duxin, H.R. Moore, J. Sidorova, K. Karanja, Y. Honaker, B. Dao, H. Piwnica-Worms, J.L. Campbell, R.J. Monnat Jr., S.A. Stewart, Okazaki fragment processing-independent role for human Dna2 enzyme during DNA replication, J. Biol. Chem. 287 (2012) 21980–21991.
[100] K.K. Karanja, S.W. Cox, J.P. Duxin, S.A. Stewart, J.L. Campbell, DNA2 and EXO1 in replication-coupled, homology-directed repair and in the interplay between HDR and the FA/BRCA network, Cell Cycle 11 (2012) 3983–3996.
[101] J. Ahn, M.V. Poyurovsky, N. Baptiste, R. Beckerman, C. Cain, M. Mattia, K. McKinney, J. Zhou, A. Zupnick, V. Gottifredi, C. Prives, Dissection of the sequence-specific DNA binding and exonuclease activities reveals a superactive yet apoptotically impaired mutant p53 protein, Cell Cycle 8 (2009) 1603–1615.
[102] S. Hampp, T. Kiessling, K. Buechle, S.F. Mansilla, J. Thomale, M. Rall, J. Ahn, H. Pospiech, V. Gottifredi, L. Wiesmuller, DNA damage tolerance pathway involving DNA polymerase iota and the tumor suppressor p53 regulates DNA replication fork progression, Proc. Natl. Acad. Sci. U. S. A. 113 (2016) E4311–4319.
[103] I. Chaudhury, A. Sareen, M. Raghunandan, A. Sobeck, FANCD2 regulates BLM complex functions independently of FANCI to promote replication fork recovery, Nucleic Acids Res. 41 (2013) 6444–6459.
[104] M. Raghunandan, I. Chaudhury, S.L. Kelich, H. Hanenberg, A. Sobeck, FANCD2, FANCJ and BRCA2 cooperate to promote replication fork recovery independently of the Fanconi Anemia core complex, Cell Cycle 14 (2015) 342–353.
[105] J.E. Yeo, E.H. Lee, E.A. Hendrickson, A. Sobeck, CtIP mediates replication fork recovery in a FANCD2-regulated manner, Hum. Mol. Genet. 23 (2014) 3695–3705.
[106] Y.H. Chen, M.J. Jones, Y. Yin, S.B. Crist, L. Colnaghi, R.J. Sims 3rd, E. Rothenberg, P.V. Jallepalli, T.T. Huang, ATR-mediated phosphorylation of FANCI regulates dormant origin firing in response to replication stress, Mol. Cell 58 (2015) 323–338.
[107] A.K. Murphy, M. Fitzgerald, T. Ro, J.H. Kim, A.I. Rabinowitsch, D. Chowdhury, C.L. Schildkraut, J.A. Borowiec, Phosphorylated RPA recruits PALB2 to stalled DNA replication forks to facilitate fork recovery, J. Cell Biol. 206 (2014) 493–507.
[108] G. Lossaint, M. Larroque, C. Ribeyre, N. Bec, C. Larroque, C. Decaillet, K. Gari, A. Constantinou, FANCD2 binds MCM proteins and controls replisome function upon activation of s phase checkpoint signaling, Mol. Cell 51 (2013) 678–690.
[109] H. Dungrawala, K.L. Rose, K.P. Bhat, K.N. Mohni, G.G. Glick, F.B. Couch, D. Cortez, The replication checkpoint prevents two types of fork collapse without regulating replisome stability, Mol. Cell 59 (2015) 998–1010.
[110] L. Incorvaia, F. Passiglia, S. Rizzo, A. Galvano, A. Listi, N. Barraco, R. Maragliano, V. Calo, C. Natoli, M. Ciaccio, V. Bazan, A. Russo, Back to a false normality: new intriguing mechanisms of resistance to PARP inhibitors, Oncotarget 8 (2017) 23891–23904.
[111] A. Errico, V. Costanzo, Mechanisms of replication fork protection: a safeguard for genome stability, Crit. Rev. Biochem. Mol. Biol. 47 (2012) 222–235.
[112] R.M. Jones, E. Petermann, Replication fork dynamics and the DNA damage response, Biochem. J. 443 (2012) 13–26.
[113] S. Minocherhomji, S. Ying, V.A. Bjerregaard, S. Bursomanno, A. Aleliunaite, W. Wu, H.W. Mankouri, H. Shen, Y. Liu, I.D. Hickson, Replication stress activates DNA repair synthesis in mitosis, Nature 528 (2015) 286–290.
[114] K.L. Chan, I.D. Hickson, On the origins of ultra-fine anaphase bridges, Cell Cycle 8 (2009) 3065–3066.
[115] K.L. Chan, T. Palmai-Pallag, S. Ying, I.D. Hickson, Replication stress induces sister-chromatid bridging at fragile site loci in mitosis, Nat. Cell Biol. 11 (2009) 753–760.
[116] Y. Liu, C.F. Nielsen, Q. Yao, I.D. Hickson, The origins and processing of ultra fine anaphase DNA bridges, Curr. Opin. Genet. Dev. 26 (2014) 1–5.
[117] C. Baumann, R. Korner, K. Hofmann, E.A. Nigg, PICH a centromere-associated SNF2 family ATPase, is regulated by Plk1 and required for the spindle checkpoint, Cell 128 (2007) 101–114.
[118] A. Biebricher, S. Hirano, J.H. Enzlin, N. Wiechens, W.W. Streicher, D. Huttner, L.H. Wang, E.A. Nigg, T. Owen-Hughes, Y. Liu, E. Peterman, G.J. Wuite, I.D. Hickson, PICH: a DNA translocase specially adapted for processing anaphase bridge DNA, Mol. Cell 51 (2013) 691–701.
[119] K.L. Chan, P.S. North, I.D. Hickson, BLM is required for faithful chromosome segregation and its localization defines a class of ultrafine anaphase bridges, EMBO J. 26 (2007) 3397–3409.
[120] C.F. Nielsen, D. Huttner, A.H. Bizard, S. Hirano, T.N. Li, T. Palmai-Pallag, V.A. Bjerregaard, Y. Liu, E.A. Nigg, L.H. Wang, I.D. Hickson, PICH promotes sister chromatid disjunction and co-operates with topoisomerase II in mitosis, Nat. Commun. 6 (2015) 8962.
[121] C. Lukas, V. Savic, S. Bekker-Jensen, C. Doil, B. Neumann, R.S. Pedersen, M. Grofte, K.L. Chan, I.D. Hickson, J. Bartek, J. Lukas, 53BP1 nuclear bodies form around DNA lesions generated by mitotic transmission of chromosomes under replication stress, Nat. Cell Biol. 13 (2011) 243–253.
[122] V. Naim, F. Rosselli, The FANC pathway and BLM collaborate during mitosis to prevent micro-nucleation and chromosome abnormalities, Nat. Cell Biol. 11 (2009) 761–768.
[123] V. Naim, T. Wilhelm, M. Debatisse, F. Rosselli, ERCC1 and MUS81-EME1 promote sister chromatid separation by processing late replication intermediates at common fragile sites during mitosis, Nat. Cell Biol. 15 (2013) 1008–1015.
[124] P. Vinciguerra, S.A. Godinho, K. Parmar, D. Pellman, A.D. D'Andrea, Cytokinesis failure occurs in Fanconi anemia pathway-deficient murine and human bone marrow hematopoietic cells, J. Clin. Invest. 120 (2010) 3834–3842.
[125] A. Madireddy, S.T. Kosiyatrakul, R.A. Boisvert, E. Herrera-Moyano, M.L. Garcia-Rubio, J. Gerhardt, E.A. Vuono, N. Owen, Z. Yan, S. Olson, A. Aguilera, N.G. Howlett, C.L. Schildkraut, FANCD2 facilitates replication through common fragile sites, Mol. Cell 64 (2016) 388–404.
[126] G. Nalepa, R. Enzor, Z. Sun, C. Marchal, S.J. Park, Y. Yang, L. Tedeschi, S. Kelich, H. Hanenberg, D.W. Clapp, Fanconi anemia signaling network regulates the spindle assembly checkpoint, J. Clin. Invest. 123 (2013) 3839–3847.
[127] S.G. Durkin, T.W. Glover, Chromosome fragile sites, Annu. Rev. Genet. 41 (2007) 169–192.
[128] H.W. Mankouri, D. Huttner, I.D. Hickson, How unfinished business from S-phase affects mitosis and beyond, EMBO J. 32 (2013) 2661–2671.
[129] R.A. Schwab, J. Nieminuszczy, F. Shah, J. Langton, D. Lopez Martinez, C.C. Liang, M.A. Cohn, R.J. Gibbons, A.J. Deans, W. Niedzwiedz, The Fanconi Anemia pathway maintains genome stability by coordinating replication and transcription, Mol. Cell 60 (2015) 351–361.
[130] A.T. Wang, T. Kim, J.E. Wagner, B.A. Conti, F.P. Lach, A.L. Huang, H. Molina, E.M. Sanborn, H. Zierhut, B.K. Cornes, A. Abhyankar, C. Sougnez, S.B. Gabriel, A.D. Auerbach, S.C. Kowalczykowski, A. Smogorzewska, A dominant mutation in human RAD51 reveals its function in DNA interstrand crosslink repair independent of homologous recombination, Mol. Cell 59 (2015) 478–490.
[131] X. Renaudin, L. Koch Lerner, C.F. Menck, F. Rosselli, The ubiquitin family meets the Fanconi anemia proteins: mutation research, Rev. Mutat. Res. 769 (2016) 36–46.
[132] S. van Twest, V.J. Murphy, C. Hodson, W. Tan, P. Swuec, J.J. O'Rourke, J. Heierhorst, W. Crismani, A.J. Deans, Mechanism of ubiquitination and deubiquitination in the Fanconi Anemia pathway, Mol. Cell 65 (2017) 247–259.
[133] J.M. Kim, K. Parmar, M. Huang, D.M. Weinstock, C.A. Ruit, J.L. Kutok, A.D. D'Andrea, Inactivation of murine Usp1 results in genomic instability and a Fanconi anemia phenotype, Dev. Cell 16 (2009) 314–320.
[134] V.H. Oestergaard, F. Langevin, H.J. Kuiken, P. Pace, W. Niedzwiedz, L.J. Simpson, M. Ohzeki, M. Takata, J.E. Sale, K.J. Patel, Deubiquitination of FANCD2 is required for DNA crosslink repair, Mol. Cell 28 (2007) 798–809.
[135] I.Y. Song, L.R. Barkley, T.A. Day, R.S. Weiss, C. Vaziri, A novel role for Fanconi anemia (FA) pathway effector protein FANCD2 in cell cycle progression of untransformed primary human cells, Cell Cycle 9 (2010) 2375–2388.
[136] S. Pathania, J. Nguyen, S.J. Hill, R. Scully, G.O. Adelmant, J.A. Marto, J. Feunteun, D.M. Livingston, BRCA1 is required for postreplication repair after UV-induced DNA damage, Mol. Cell 44 (2011) 235–251.
[137] S. Guillemette, A. Branagan, M. Peng, A. Dhruva, O.D. Scharer, S.B. Cantor, FANCJ localization by mismatch repair is vital to maintain genomic integrity after UV irradiation, Cancer Res. 74 (2014) 932–944.
[138] K.D. Mirchandani, R.M. McCaffrey, A.D. D'Andrea, The Fanconi anemia core complex is required for efficient point mutagenesis and Rev1 foci assembly, DNA Repair 7 (2008) 902–911.

Please cite this article in press as: M.B. Federico, et al., Beyond interstrand crosslinks repair: contribution of FANCD2 and other Fanconi Anemia proteins to the replication of DNA, Mutat Res Fund Mol Mech Mutagen (2017), http://dx.doi.org/10.1016/j.mrfmmm.2017.09.004