

REVIEW

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Fanconi anemia pathway as a prospective target for cancer intervention

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Abstract

Fanconi anemia (FA) is a recessive genetic disorder caused by biallelic mutations in at least one of 22 FA genes. Beyond its pathological presentation of bone marrow failure and congenital abnormalities, FA is associated with chromosomal abnormality and genomic instability, and thus represents a genetic vulnerability for cancer predisposition. The cancer relevance of the FA pathway is further established with the pervasive occurrence of FA gene alterations in somatic cancers and observations of FA pathway activation-associated chemotherapy resistance. In this article we describe the role of the FA pathway in canonical interstrand crosslink (ICL) repair and possible contributions of FA gene alterations to cancer development. We also discuss the perspectives and potential of targeting the FA pathway for cancer intervention.

Keywords: Fanconi anemia, DNA repair, Tumorigenesis, Cancer intervention

Introduction

Normal cells harbor a delicate system of DNA damage sensing and repair to overcome a variety of DNA lesions that otherwise elicit genome instability and cellular toxicity if not repaired properly [1, 2]. A hallmark of many cancers is genome instability which results from dysregulation of DNA damage sensing and repair [3]. Clonal selection of advantageous mutation carriers with compromised cell cycle checkpoint, constitutive proliferative signaling, or dysfunctional cell death constitutes the onset of somatic carcinogenesis [4]. Meanwhile, elevated or rewired DNA repair networks function as caretakers to handle excessive DNA damage and replicative stress resulting from rapid cancer cell proliferation. This reprogramming is frequently found to be associated with resistance to common chemotherapies [5]. The Fanconi anemia (FA) pathway is known for its role in DNA interstrand crosslink (ICL) repair [6]. In addition to its

pathological relevance to the genetic disorder of Fanconi anemia, the FA pathway has been overwhelmingly positioned in the context of cancer [7, 8], suggesting that targeting the FA pathway is a prospective avenue for cancer intervention.

The FA pathway and interstrand crosslink repair

ICLs are a class of DNA lesions that can be introduced both endogenously and exogenously. Aldehydes, which are produced by many metabolic processes such as lipid peroxidation, histone demethylation, and alcohol metabolism, cause the formation of ICLs [9–12]. Common chemotherapeutic agents such as mitomycin C and platinum are DNA crosslinkers that introduce both intrastrand crosslinks and ICLs. While intrastrand crosslinks are readily repaired by the nucleotide excision repair (NER) pathway [13], ICLs represent a highly cytotoxic lesion that is primarily repaired by the FA pathway [14]. Fanconi anemia is a rare genetic disorder caused by biallelic mutations in one of the 22 known FANC genes [15–21]. Affected patients have deficient ICL repair. Clinical diagnosis of FA can be performed through observation of elevated chromosomal rearrangements (predominately radial chromatids) within

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patient derived cells after treatment with an ICL-inducing agent such as Diepoxybutane [22, 23]. The 22 FANCD1 proteins along with many FA associated factors work together to recognize ICL damage, activate the pathway by FANCD1-FANCD2 (ID2) monoubiquitination, and initiate downstream double-strand break (DSB) repair.

ICL recognition and the FA core complex

ICLs that occur outside of S phase are sensed and repaired by the NER pathway [14]. The FA pathway-mediated ICL repair occurs primarily in S phase and starts with the formation of an X shaped DNA structure that occurs upon convergence of two head-on replication forks surrounding the ICL site [24, 25] (Fig. 1a). The

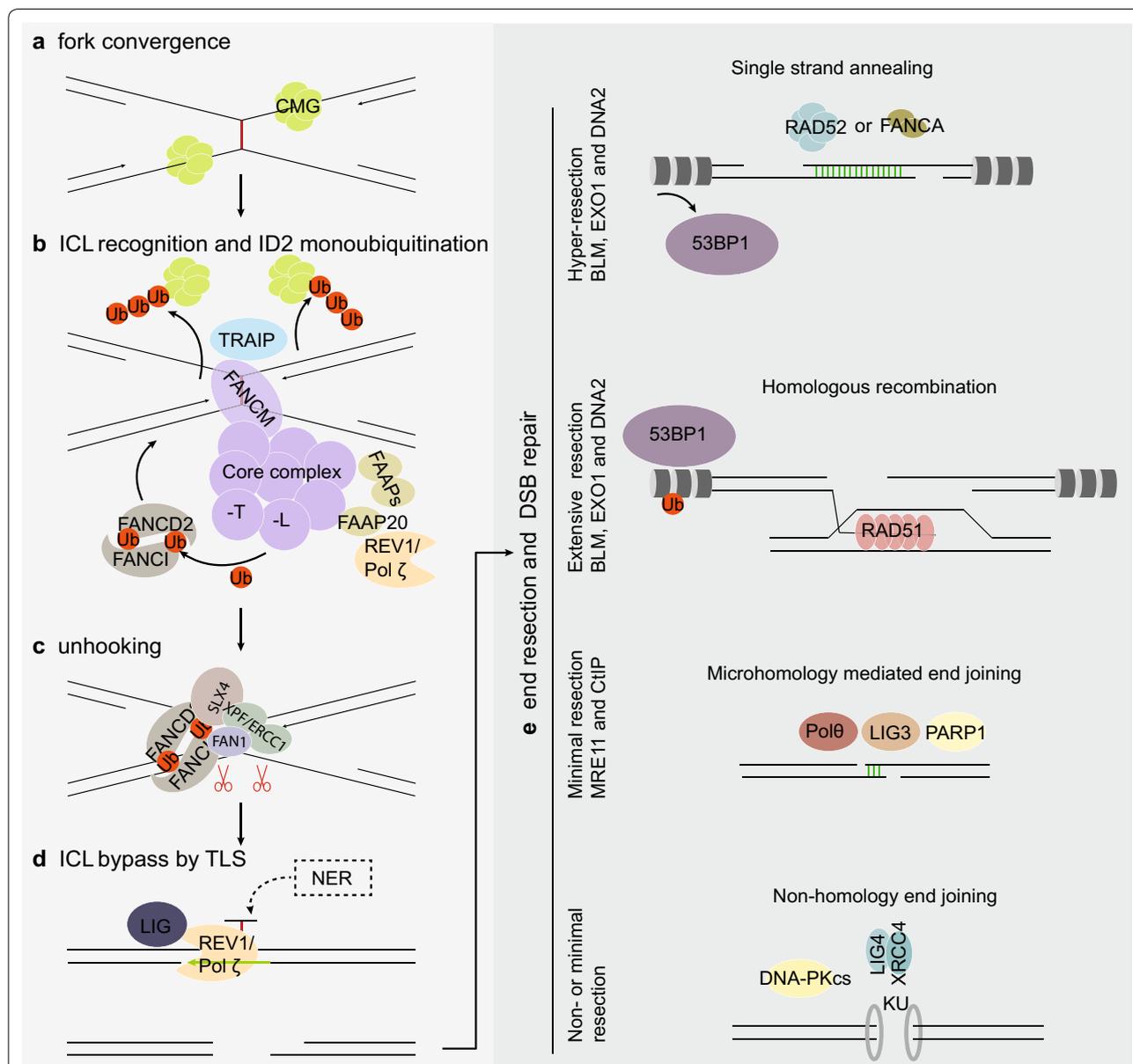


Fig. 1 The Fanconi anemia pathway of DNA repair. **a** Repair of ICL in replicative phase starts with convergence of two replication forks surrounding the ICL site. **b** FANCD1/FAAP24 complex recognizes the X shaped DNA structure and recruits other members of the FA core complex and FAAPs. Monoubiquitination of the ID2 complex represents the step of activation of the FA pathway. **c** ID2 recruits FANCD1 and structure specific nucleases for incision surrounding the ICL sites to unhook the damage. **d** Translesion synthesis polymerases REV1/pol ζ bypass the unhooked ICL damage. The unhooked ICL remnant will be subsequently repaired by NER. **e** Double strand break intermediates can be repaired via four sub-pathways of DNA DSB repair depending on the result of end resection

CMG (Cdc45-MCM-GINS) helicase complex is ubiquitinated by the E3 ubiquitin ligase TRAP [26]. Short ubiquitin chains recruit NEIL3 glycosylase for incision-independent unhooking mechanism of ICL resolution. Long ubiquitin chains promote CMG unloading from the chromatin in a p97 dependent manner [26, 27] which allows further approach of the two replication forks toward the ICL (Fig. 1b), and commitment to Fanconi anemia pathway-mediated ICL repair. It has been demonstrated that the FANCM/FAAP24 complex recognizes the ICL lesion and initiates recruitment of other components of the FA core complex [28] (Fig. 1b). The FA core complex assembles through several sub-complexes: FANCA-FANCG-FAAP20, FANCE-FANCF-FANCC, FANCB-FANCL-FAAP100 [29–33], and other FAAPs. A most recent structural study described an 8-FA-protein core complex that assembled surrounding the scaffold comprised of two central heterodimers of FANCB and FAAP100. FANCB and FAAP100 adopt similar structure despite limited sequence homology [30]. Two RING finger FANCL subunits flank the FANCB-FAAP100 scaffold in different conformations suggesting functional asymmetry. Selective incorporation of the E2 ubiquitin-conjugating enzyme UBE2T (FANCT) into the core complex by the E3 ubiquitin ligase FANCL determines substrate specificity and modification type [34]. Mutations or loss of any core complex components lead to diminished monoubiquitination activity and thus inefficient activation of the FA pathway. As the activation signal in the FA pathway, FANCD2 and FANCI (ID2) are monoubiquitinated on Lysine-561 and -523 respectively [35–38] by FANCL and UBE2T. The most recent structure-based study suggests that the monoubiquitination of FANCD2 during DNA repair stabilizes a closed clamp conformation of the FANCI-FANCD2 complex [39]. Under non-damaging conditions, accessibility to these residues are buried in the complex. Damaging conditions allow guidance from ATR-CHK1-mediated FANCI phosphorylation that promotes ID2 dissociation and interface exposure [40, 41] (Fig. 1b). Meanwhile, modification of FANCD2 allows a functional switch where a cluster of phosphorylation sites between residues 882 and 898 are substrates of casein kinase 2 (CK2) [42]. Upon completion of ICL repair FANCD2 is deubiquitinated by chromatin bound USP1-UAF1-RAD51AP1 complex and released from the initial damage site for the next round of repair events [43–45].

Unhooking and translesion synthesis (TLS)

FANCD2 binds to H4K20me2 via its histone-binding domain (HBD) and an embedded methyl-lysine-binding domain (MBD). A HBD/MBD mutant of FANCD2 that can be efficiently monoubiquitinated demonstrates

impaired chromatin binding and foci formation, suggesting that monoubiquitination precedes ICL recruitment of FANCD2 [46]. However, arguing against this time course are studies that showed the ID2 complex is recruited to ICLs before the occurrence of FANCD2 monoubiquitination [41]. Nevertheless, ubiquitinated ID2 complex is required for the recruitment of structure specific endonucleases (SSEs) and translesion synthesis (TLS) polymerases for downstream repair [47]. Removal of the ICL starts with nucleolytic cleavage at stalled forks to incise the ICL on one parental strand, a process known as unhooking (Fig. 1c). ERCC1/XPF (FANCO), MUS81/EME1, and FAN1 have been implicated as necessary for ICL incision [2, 14, 48–60]. SLX4 (FANCP) is the master scaffold and regulator of ERCC1/XPF, MUS81/EME1/2, and SLX1 nucleases for ICL processing [7]. SLX4 enters the ICL site through its N-terminal ubiquitin-binding zinc finger (UBZ) domain [61] and further recruits and activates the ERCC1/XPF (FANCO) endonuclease activity [62]. The mechanism for selective recruitment of downstream nucleases by SLX4 remains elusive. Nevertheless, a recent study suggests that SLX4IP, a constitutive member of the SLX4 complex promotes ERCC1/XPF incorporation [63].

Following unhooking, the ICL remnant on one parental strand becomes a roadblock for replicative polymerases. Translesion synthesis polymerases are thus recruited to the ICL site by the FA core complex [64] for damage bypass. A dCMP transferase Rev1 first inserts a dCMP opposite the unhooked ICL and extension of the DNA synthesis is carried out by pol ζ [64, 65]. Damage-induced mutations are introduced surrounding the ICL position with a mutation frequency of ~1% [64]. NER mediated removal of the ICL remnant on the parental strand completes the repair (Fig. 1d). The other DNA duplex with a DSB is ultimately repaired by multiple DSB repair sub-pathways.

DSB repair through HR and other sub-pathways

DNA DSBs can be repaired through four coexisting sub-pathways, namely homologous recombination (HR), single strand annealing (SSA), microhomology-mediated end joining (MMEJ), and non-homologous end joining (NHEJ) that require differentially resected DSB ends and different levels of homology [66, 67] (Fig. 1e). Ku proteins readily bind minimally- or non- resected DSBs based on their abundance and low K_d for DNA ends [68–70], and recruit DNA-dependent protein kinase (DNA-PKCs) and DNA ligase-4 (LIG4) to carry out non-homologous end joining (reviewed in [24]). Alternatively, a DSB undergoes progressive end resection. MRE11 and CtIP nucleases generate minimally resected DSB ends with 3' ssDNA. Helicases and exonucleases BLM, EXO1 and DNA2 are

brought in to produce extensively resected DSB ends [71]. Further resection is prevented by the presence of chromatin bound 53BP1 and 53BP1-recruited assembly of RIF1, REV7, PTIP, and Artemis [72]. Hyper-resection occurs when 53BP1 is unloaded from chromatin flanking the DSB. These differentially processed DSB ends are preferred substrates for MMEJ [73], HR, and SSA [74] respectively (Fig. 1e).

HR and NHEJ have been known as the two subpathways of DSB repair that are more relevant for FA pathway-mediated ICL repair. Among the 22 FA complementation groups a large number are well-established HR factors. HR is known as the preferential pathway over error-prone end joining for the repair of DSB intermediates that occur during ICL repair (reviewed in [20, 75]). This opinion is supported by the readily available HR compatible template (the repaired DNA duplex) that occurs at ICL sites, and many other experimental observations. Monoubiquitinated FANCD2 has been shown to interact with CtIP nuclease [76], one of the early exonucleases needed to initiate end resection of DSBs and disable NHEJ. FA pathway deficiency not only causes reduction in HR efficiency in the DR-GFP assay [77, 78], but also leads to increased deleterious repair through NHEJ, which is largely responsible for the translocations and abnormal chromatin structures observed in FA patient cells [75]. Accordingly, ICL sensitivity can be rescued by inhibition of many NHEJ factors in many FA deficiency models including *C. elegans*, chicken DT40 cells, mouse embryonic fibroblasts and human cells where FA components were knocked down, knocked out, or mutated [79, 80]. Besides these two subpathways, SSA may also participate in ICL and DSB repair via the newly identified strand annealing activity of FANCA [66, 81, 82].

The relevance of the FA pathway to cancer

Blood and bone marrow stem cell transplants are the most effective treatment for various Fanconi anemia cases and confer significant improvement for quality of life and lifespan of FA patients. A significant cause for the death of FA patients has shifted to cancer development associated with failure of the FA repair pathway. A most recent survey of 111 FA patients indicates a cancer frequency of 30%. Intriguingly FA-A patients develop cancer at the age of 18.5 (mean), significantly older than 5.2 (mean) for the other complementation groups [83]. Myeloid leukemias, liver tumors, head and neck carcinomas, and gynecologic malignancies are the most profound predisposing cancers among FA patients [7, 84]. Sequencing studies and FISH analysis have shown that amplifications of certain oncogenes

due to chromosomal instability are at least partially responsible for blood cancers in FA patients [85].

Over the last two decades, many Fanconi anemia mouse models have been employed to study the pathology, and explore the clinical managements of FA (see reviews [86, 87] with systematic survey of early mice studies). While cells derived from knockout mice recapitulate the phenotypes of FA patient cells in general, these mice also partially reproduce the pathological characteristics of FA patients especially for the hematological abnormality and cancer occurrence, albeit with lower onset incidence and dissimilar cancer types. This allows valuable evaluations of chemo- and radio-therapy efficacy for cancers and genotoxicity alleviation in FA patients as FA carriers are hypersensitive to DNA lesions.

Beyond the disease of Fanconi anemia, more intriguingly somatic alteration of FA genes has been widely characterized in cancer tissues by large scale sequencing. The role of FA genes in cancer development is discussed below.

The FA pathway protects cells from R-loop accumulation and genome instability

Genome instability is a hallmark of cancer [88]. The FA pathway is a major player for the maintenance of genome stability through DNA damage repair, replication fork stabilization, and oxidative and mitotic stress alleviation (see our previous comprehensive review [75] and [7]). A R-loop is a 3-stranded DNA:RNA hybrid structure produced co-transcriptionally. R-loop formation represents a cellular process for gene expression regulation as well as a major source of genome instability [89–92]. R-loop accumulation largely results in and from collisions that occur between replication forks and the transcriptional machinery in a head-on orientation [93]. One emerging function of the FA pathway is to protect cells from R loop accumulation and its associated genome instability. Both human and murine FA deficient cells (FA-A, FA-D2, FA-M) exhibit elevated levels of R-loops and genome instability [92, 94]. Monoubiquitination of FANCI-FANCD2 complex can be enhanced upon their binding of both RNA and R-loop substrates in vitro [95]. It has been shown that RNA processing factors such as hnRNP-U and DDX47 are recruited by FANCD2 for R-loop resolution [96, 97]. Besides RNaseH1, a predominant factor for efficient R-loop removal, an alternative resolution of R-loop is through the translocase activity of FANCM, as FANCM catalyzes displacement of RNA from the R-loop structure [94]. These data suggest that many FA components or the whole FA pathway participate in R-loop suppression.

Association of FA alterations with somatic cancer

Beyond germline mutations in FA patients, sporadic alterations of FA genes are frequently found in many cancers. A brief survey of cases in the NIH GDC portal reveals that over 65% of the 10,202 listed cancers have

at least one alteration of one of the FA genes (mutation, gain or loss) (Fig. 2a). Alterations of FANCA, FANCC and FANCG are the most predominately observed FA mutations and account for over 80% of Fanconi anemia patient cases. Simple somatic mutation (SSM) frequency

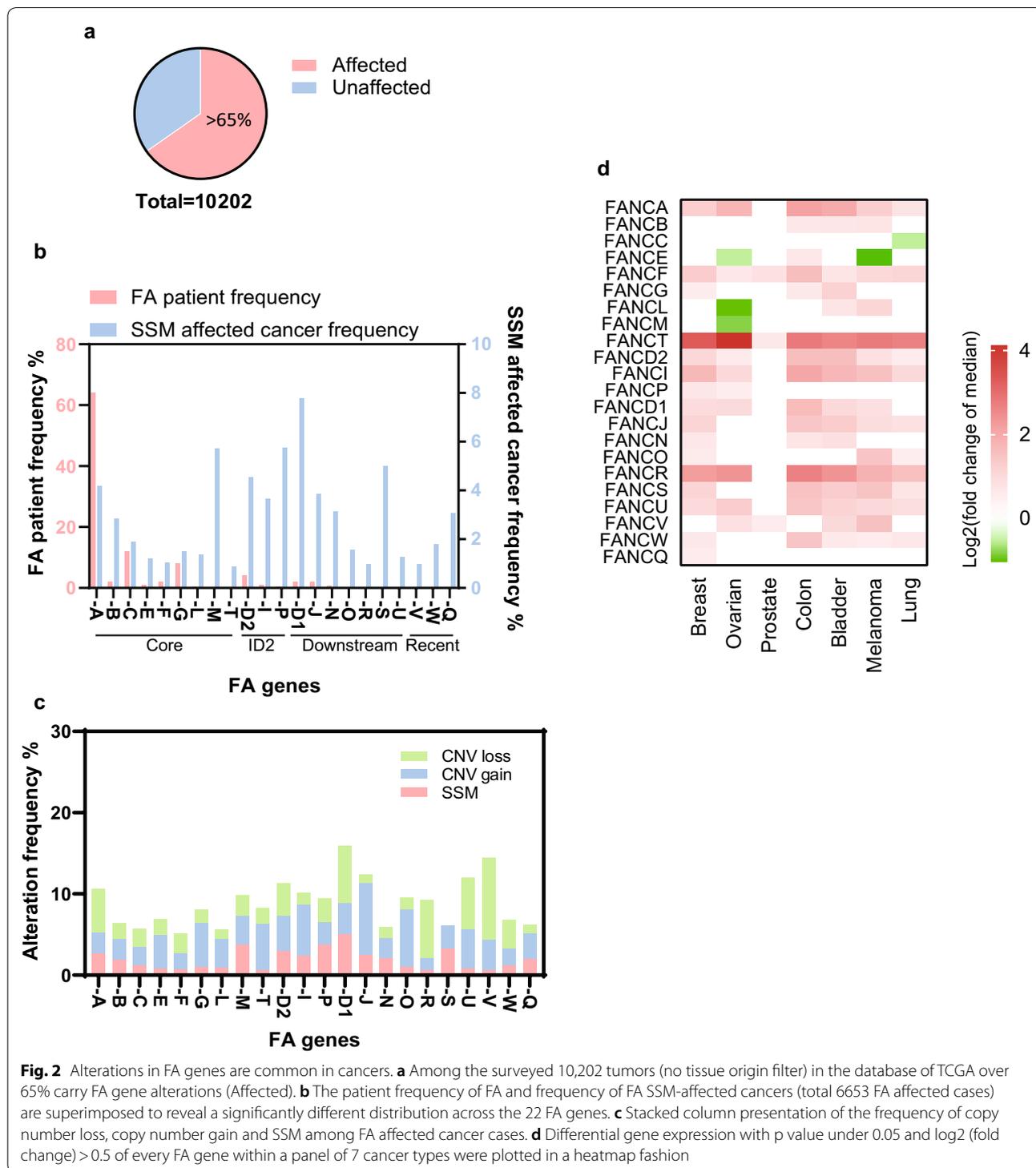


Fig. 2 Alterations in FA genes are common in cancers. **a** Among the surveyed 10,202 tumors (no tissue origin filter) in the database of TCGA over 65% carry FA gene alterations (Affected). **b** The patient frequency of FA and frequency of FA SSM-affected cancers (total 6653 FA affected cases) are superimposed to reveal a significantly different distribution across the 22 FA genes. **c** Stacked column presentation of the frequency of copy number loss, copy number gain and SSM among FA affected cancer cases. **d** Differential gene expression with p value under 0.05 and log₂ (fold change) > 0.5 of every FA gene within a panel of 7 cancer types were plotted in a heatmap fashion

of FA genes in the cancer population shows a rather even distribution among FA genes, with modest elevation in the ID2 complex, FANCA and FANCM of the core complex, and some downstream HR components (Fig. 2b). This discrepancy in mutation distribution in cancer and Fanconi anemia suggests that molecular actions of FA genes during FA development and cancer development are different.

Two-tier contribution of the FA pathway to cancer

In addition to mutations, copy number changes (both gain and loss) of FA genes are also commonly present in cancer (Fig. 2c). Meanwhile, a survey of differential gene expression (tumor vs normal) of individual FA genes by using tumors and tissues from the TCGA and GTEx database, respectively, clearly indicates overexpression of most FA genes across a variety of cancer types (Fig. 2d). Consistent with the prevalent upregulation of almost all FA genes in cancer, is that FA gene expression receives coordinated regulation through the Rb/E2F pathway [98]. The coexistence of both gain (copy number increase and RNA expression increase) and loss (copy number loss and mutations) of function alterations for almost every FA gene with no obvious preference suggests that the distribution of FA genes to cancer is two-tier. On one hand, deficient FA pathway and rerouted damage repair pathways cause genome instability and “mutator phenotype” resulting in accumulation of mutations, deletions and translocations that constitute the starting pool for tumorous clonal selection. On the other hand, elevation of FA gene expression and thus DNA damage repair capacity is beneficial for mitigating excess DNA lesions and chromosomal abnormalities that accompany fast proliferation of cancer cells [5]. This divergence is reconciled under a model of biphasic requirement of the FA pathway throughout the initiation and progression of cancer, reminiscent of stage-specific alteration of FANCF expression by promoter methylation in ovarian cancer [99].

Transcriptional regulation functions of FA proteins

In addition to ICL repair, a handful of studies also imply that the FA pathway is involved in transcriptional regulation that may contribute to cancer development. The FA core complex interacts with transcriptional repressor Hairy Enhancer of Split 1 (HES1) [100], binds to the HES1 promoter, and regulates HES1 responsive genes directly and indirectly [101]. FANCC regulates nuclear translocation of β -catenin and works as a transcriptional repressor of β -catenin downstream gene DKK1 [102]. Besides these case studies, An RNA-seq study revealed a collection of genes with altered expression among which a large portion are implicated in oncogenic processes [103]. Further studies are needed to explore the potential

transcriptional regulation role of FA proteins especially in cancer contexts where FA gene expression is found to be high.

The FA pathway as a prospective target for cancer intervention

Association of the FA pathway with drug resistance

One way for cancer cells to become refractory to DNA damage-inducing chemotherapy is through acquisition of higher DNA damage repair capacity. Platinum based compounds, such as cisplatin, have been widely used to treat various cancers [104]. However, their potency is often challenged by acquired resistance [104–106]. Elevation of FA gene expression is pervasive in cancers (Fig. 2a) and is frequently found to be associated with chemo-resistance. A subset of ovarian cancer cell lines with FANCF methylation are hyper-sensitive to cisplatin while FANCF complementation in these cells restores resistance [99]. Similar resistance has also been found in the subset of cell lines harboring aberrant demethylation of the FANCF gene [99]. An A549 NSCLC cell derived cisplatin resistant cell line A549/DR exhibits upregulation of multiple FA genes and elevated FANCD2 monoubiquitination compared to its parental and other NSCLC lines [107]. Knock down of FA genes successfully re-sensitizes A549/DR cells to cisplatin treatments. Meanwhile, enhanced FA pathway activation has also been shown to be associated with resistance to melphalan in multiple myeloma [108] and pancreatic cancers [109]. In addition to DNA crosslinkers, the FA pathway also confers resistance to DNA alkylating agents in glioma [110]. Alongside FA-mediated drug resistance are observations that FANCA and FANCT/UBE2T correlate with poor prognosis and survival of cancer patients [111, 112]. These pre-clinical data highlight the need for development of FA targeted drugs in circumstances where chemotherapy resistance emerges as a result of elevated FA pathway expression and function.

Exploring the FA pathway for synthetic lethality

When one cellular function is dependent on multiple pathways in parallel, activation of either pathway can be sufficient for the fulfillment of this function, and thus cell viability. Disruption of one pathway frequently enhances cell dependency on compensatory pathways. Inactivation of isolated DNA repair pathways and its associated genome instability is a common hallmark for cancer and crucial for cancer initiation and promotion [113, 114]. High levels of association of cancer types to deficiency in DNA repair pathways are widely known: FA/HR pathway (BRCA1, BRCA2, PALB2) for breast, ovarian and prostate cancer; mismatch and base excision repair (MSH2/6, MUTYH) for colorectal cancer; DNA

damage response (DDR) genes (ATM) for leukemia and etc. Inactivation of these pathways provides a prominent advantage to use the synthetic lethal approach for treatments. The most successful practice of synthetic lethality is using PARP (poly (ADP-ribose) polymerase) inhibitors for BRCA deficiency-carrying cancers [115]. Abrogation of SSB repair by PARP targeting causes overwhelming DSB accumulation during replication that cannot be effectively resolved through the homologous recombination pathway and eventually leads to cytotoxic DNA abnormalities as a product of non-faithful end joining [116]. This approach confers lower systematic toxicity than traditional chemotherapies as normal cells survive the PARP inhibition when they are out of cell cycle and maintain functional homologous recombination capability. In addition to the BRCA deficient gynecologic cancers, PARP synthetic lethality has shown effectiveness with PTEN mutated cancers [117, 118], although the mechanism remains to be studied [119].

Multiple genes of the FA pathway have been highly ranked as genes of interest with synthetic lethality potential in a computational study [120]. siRNA screening reveals many genes, TREX2, PARP1, PLK1, UBE2B, ATM and more are synthetic lethal with FA deficiency [121]. Experimental models of both human fibroblasts and murine embryonic fibroblasts with FA pathway deficiency are hypersensitive to ATM inhibition [121]. Moreover formaldehyde catabolism has been shown as a prospective target for FA deficient cells to achieve synthetic lethality [122]. While the FA pathway synthetic lethality relationships are still under evaluation, these studies do encourage an inclusion of FA genes as part of tumor mutation screening for possible treatment strategy based on synthetic lethality. Vice versa, suppression of the FA pathway by FA targeting intervention is plausible for killing of cancer cells with deficiencies in synthetic lethal partner pathways of the FA pathway.

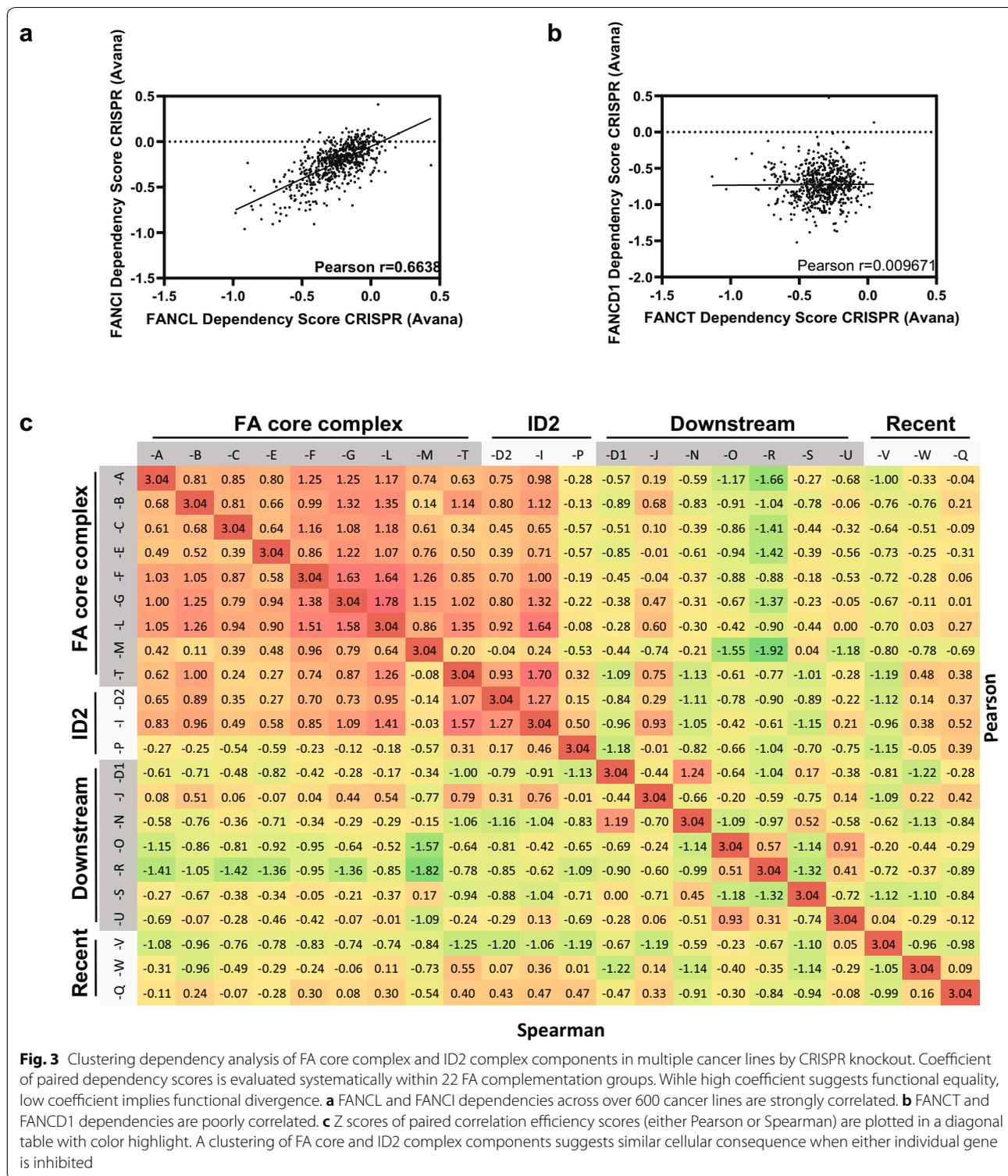
Targeting the FA pathway with FA specific inhibitors

The FA pathway is composed of 22 FA proteins and many FAAPs and operates in a progressive multistep manner. Will targeting any member impact cancer survival? To answer this question we set out to survey dependency scores (experimental measurement of genetic vulnerabilities by using CRISPR) of every FA genes within a panel of over 600 cancer cell lines of various tissue origins by using the depmap portal (<https://depmap.org/portal/>, [123]). While all the 22 FA genes alone exhibit only low to modest cancer cell dependency in general, considerable pairs of FA genes display highly correlated (Pearson $r > 0.5$) dependency across cell lines, such as the pair of FANCL and FANCL (Pearson $r = 0.664$, Fig. 3a) suggesting similar consequence when either one is inhibited.

Nevertheless, low or non-correlation is also observed for many FA gene pairs, such as FANCT and FANCD1 (Pearson $r = 0.010$, Fig. 3b). When the correlation coefficients are plotted as Z scores and color highlighted, a cluster of FA genes emerges with mutually correlated dependency that comprise FA core complex and ID2 genes (Fig. 3c). This suggests comparable, if not the same outcomes can be achieved when either gene in the cluster is inhibited. Targeting members in this cluster is preferable if FA-specific effects are demanded. Divergent dependency patterns of the downstream and recently discovered FA genes reflects the complexity of these genes' role in FA nonspecific pathways. Targeting these members might be beneficial when additional or wide spectral outcomes are favored.

While both chemotherapy re-sensitization and synthetic lethality will benefit from FA targeting inhibitors, no widely accepted FA specific therapeutic compound exists. Proteasome inhibitors are known to inhibit damage-induced FANCD2 foci formation, albeit through an unclear mechanism [124]. A few natural compounds including curcumin and its derivatives have been identified as FA pathway inhibitors through cell-based [105, 125] and *Xenopus* egg extract-based screening [126]. Meanwhile HSP90 facilitates FA pathway function as FANCA is a client of HSP90 and needs HSP90 interaction for stability [127]. HSP90i and withaferin A abrogate DNA damage-induced FA activation [128]. These inhibitors are capable of chemotherapy sensitization to cross-link-like damage [105, 124, 126]. However, only a handful of FA protein targeting compounds have been described (summarized in Table 1). Discovery of novel FA specific inhibitors with improved binding kinetics and FA pathway disruption is in demand. According to Fig. 3, rational inhibition of core complex and ID2 proteins are likely to sensitize cells to FA-specific impacts whereas the intervention at downstream members will be possibly beneficial for a variety of other pathways.

Multiple approaches can be employed for the development of FA specific inhibitors. Among the 22 FA genes, 13 have partially resolved structural data (alone, or complexed with other complementation groups, summarized in Table 1) that could facilitate rational design of small molecular compound leads. For instance, structural perturbation surrounding ERCC1 Phe293 is sufficient for its disruption of its interaction with XPF according to mutagenesis data [129, 130] and available structures (Table 1). Moreover, complex and functional unit formation in vitro and in vivo can be utilized for screening of interaction-disrupting compounds given proper design of compatible high throughput assays, such as fluorescence activation or FRET. In addition, a few FA proteins possess particular biochemical activities including strand



annealing and strand exchange activity of FANCA, ubiquitin conjugation or ligation of FANCL, FANCT and FANCW, helicase activity of FANCL, and even DNA binding activity of multiple FA proteins (summarized in

Table 1) whose proper reconstitution in vitro can expedite drug discovery eminently. For instance, in vitro reconstitution of E1, E2/FANCT, E3/FANCL cascades has been successful in finding two hits that reduce

Table 1 A summary of reported FA proteininhibitors and available structures or biochemical activities to facilitate drug development

FA genes	Protein structures	Molecular activities	Inhibitors	References
FANCA	6LHS	DNA binding, strand annealing and exchange	HSP90i including withaferin A	[66, 81, 128, 132]
FANCF	2IQC		Natural compounds from <i>Wrightia religiosa</i>	[133, 134]
FANCL	3ZQS, 4CCG	E3 ligase	CU1, CU2	[34, 131, 135]
FANCM	4BXO, 4DAY, 4DRB, 4E45, 4M6W	DNA binding	MM2 peptide	[136–141]
FANCT/UBE2T	1YH2, 4CCG, 5NGZ, 5OJJ	E2	A few leads by fragment screening	[34, 142–144]
FANCD2	3S4W	DNA binding		[145]
FANCI	3S51	DNA binding	Undisclosed	[146, 147]
FANCP/SLX4	4M7C, 4UYI, 4ZOU	DNA binding		[148]
FANCD1/BRCA2	1N0W, 3EU7	DNA binding	Antisense oligonucleotide (ASO)	[149–151]
FANCI/BRIP1	1T15, 1T29, 3AL3	Helicase		[152–154]
FANCN/PALB2	2W18, 3EU7	DNA binding		[150]
FANCO/RAD51C		DNA binding		
FANCR/RAD51	1B22, 1N0W, 5H1B, 5H1C, 5JZC, 5NP7, 5NWL	Strand exchange	RI-1, RI-2, B02, CYT01A	[149, 155–161]
FANCS/BRCA1	1JM7, 1JNX, 1N5O, 1OQA, 1T15, 1T29, 1T2U, 1T2V, 1Y98, 2ING, 3COJ, 3K0H, 3K0K, 3K15, 3K16, 3PXA, 3PXB, 3PXC, 3PXD, 3PXE, 4FI, 4IGK, 4JLU, 4OFB, 4U4A, 4Y18, 4Y2G, 6G2I	DNA binding		[152, 153, 162–174]
FANCV/REV7	3ABD, 3ABE, 3VU7, 4EXT, 4GK0, 4GK5, 5XPT, 5XPU, 6BC8, 6BCD, 6BI7	DNA binding	REV7 specific compounds	[175–180]
FANCW/RFWD3	6CVZ	E3		
FANCO/XPB	1Z00, 2A1J, 2AQ0, 2KN7, 2MUT	DNA incision		[181–185]

FANCD2 foci formation and synergize with carboplatin for cancer cell killing [131].

Conclusion

Cancer predisposition is a common genetic vulnerability beyond anemia and bone marrow failure in FA patients with inherent biallelic alterations in FA genes. Observation and association of loss of function of FA genes by means of genetic alteration and repressed transcription in many somatic cancers implies that FA inactivation may represent a more pervasive avenue for combating the onset of cancer development. Many preclinical studies demonstrated that treatment of this subtype of cancer is more effective through the approach of synthetic lethality. On the other hand, elevated FA function through gene copy increase or transcriptional regulation is a prevalent phenotype of a large cancer population and is widely associated with intrinsic or acquired resistance to ICL-inducing chemotherapy. For effective and novel treatments of cancers with FA alteration, incorporation of FA gene mutation status into tumor mutation

screening and development of FA specific inhibitors are in demand.

Abbreviations

FA: Fanconi anemia; BER: Base excision repair; NER: Nucleotide excision repair; CIN: Chromosomal instability; ICL: Interstrand crosslink; NHEJ: Non-homologous end joining; MMEJ: Microhomology mediated end joining; DDR: DNA damage response; SSA: Single-stranded annealing.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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