HHS Public Access

Author manuscript

Cancer Cell Microenviron. Author manuscript; available in PMC 2015 December 02.

Published in final edited form as:

Cancer Cell Microenviron. 2015 ; 2(4): . doi:10.14800/ccm.986.

Advances in the understanding of Fanconi Anemia Complementation Group D2 Protein (FANCD2) in human cancer

Yihang Shen[1], **Jun Zhang**[2], **Herbert Yu**[3], and **Peiwen Fei**[1]

[1]Divisions of Cancer Biology University of Hawaii Cancer Center, University of Hawaii, Honolulu, HI, USA

[2]Department of Laboratory Medicine and Pathology, Mayo Clinic, MN, USA

[3]Divisions of Epidemiology, University of Hawaii Cancer Center, University of Hawaii, Honolulu, HI, USA

Abstract

Fanconi anemia (FA) is a rare human genetic disease, resulting from dysfunction in any of 17 known complementation proteins: FANC-A, B, C, D1, D2, E, F, G, I, J, L, M, N, O, P, Q & S, and other unknowns. Besides the severe bone marrow failure, an extremely high incidence of cancer as well as many other clinic symptoms associated with FA patients, FA cells are known of insufficiency in homologous recombination, DNA mismatch repair, nucleotide excision repair, translesion DNA synthesis, and other molecular defects, leading to genome instability. Those similar molecular and cellular/tissue features show that all FA proteins function in one common signaling pathway, namely, the FA pathway. The monoubiquitination of FANCD2 is the central step of the FA pathway activation upon DNA damage or during DNA replication. The molecular functions of FANCD2 emerge as a very attractive filed of investigation in cancer research. Herein, we review the recent progresses in FANCD2 functions at these rapidly progressed aspects.

Keywords

FANCD2; Replication; Gain of Function; DNA damage; Tumor cell sensitivity

Introduction

Fanconi anemia (FA) is a rare hereditary disease, characterized by an extremely high incidence of both hematological and non-hematological malignancies and multiple developmental defects[1–6]. Cells from FA patients display a chromosome breakage and hypersensitivity to DNA crosslinking agents such as mitomycin C (MMC), diepoxybutane (DEB) or cisplatin[7, 8]. Now it has been widely acknowledged that 17 complementation groups [FANC-A, B, C, D1 (BRCA2), D2, E, F, G, I, J (BRIP1), M, N (PALB2), O (RAD51C), P (SLX4), Q (ERCC4) and S (BRCA1)][1, 5, 6, 9–18] and other unknowns define a multicomponent FA pathway involved in cellular responses to DNA damage and replication.

Correspondence: Peiwen Fei, Pfei@cc.hawaii.edu.

Sequence database of homologs in different species reveal that FANCD2 may determine a highly conserved and central function of a cellular signaling pathway, evolving into a fine-tuning multiple-player one in humans. FANCD2 may function either in upstream, downstream or independent of the multi-FA protein complex[19]. So far, the crucial roles of FANCD2 playing in the FA pathway are attracting more and more attention. The dysfunction of FANCD2 derived from genetic mutation either hetero- or homozygosity has been detected in a variety of cancers[20–23] and concluded to be positively correlated with cancer development[24]. Herein, we review recent studies on the underlying mechanisms of FANCD2 in the suppression of tumor development.

Ubiquitin modulation for FANCD2 activation

The activation of the FA pathway has been well revealed by the findings that K561 of FANCD2 and K523 of FANCI are monoubiquitinated by the FA complex E3 ubiquitin ligase to form a heterodimer[25–27], which aggregate with the downstream proteins in nuclear foci to exert DNA crosslink and/or double DNA strand break (DSB) repair[28]. The current studies mainly focus on elucidating the modulation of FANCD2 monoubiquitination/activation.

In a defective FA pathway model of non-FA Calu-6 lung cancer cells, we found that FANCL expression was at a low level after examining the levels of FA complex proteins, which perform E3 ubiquitin ligase activity. This complex E3 is required for the monoubiquitination of FANCD2 or the activation of the FA pathway, indicating that the reduced FANCL expression can represent the functional heterozygosity of the FA pathway[29]. Besides FANCL, we also found a novel tumor promotion factor named "FAVL", meaning for a variant of FANCL, was highly expressed in Calu-6 lung cancer cells and in nearly 50% of 130 tested cancer tissue samples. Further, we revealed that a decreased FANCL expression in the nucleus results from its cytoplasmic retention induced by FAVL, enhancing FANCL's degradation[30]. Importantly, FAVL impairment of the FA pathway promotes a growth advantage for cancer cells and their genome instability *in vitro*, and thus tumor development represented by a xenograft mouse model. This study, for the first time, indicates that the impaired FA pathway triggered by FAVL contributes to the development of cancers in patients without FA and therefore adds a new challenging layer of complexity to human tumorigenesis[6, 30, 31].

The biallelic mutation or deficiency of UBE2T, the primary E2 conjugating enzyme contributing to the activation of FA pathway/the monoubiquitination of FANCD2 has been considered to be a new FA complementation group protein "FANCT", and reported to cause FA subtype *in vivo*[32]. The defective UBE2T protein with mutations, such as Ala157Cys, Gln2Glu[32, 33] or exon deletions[34] abolishes FANCD2 monoubiquitination and the formation of foci after MMC or other DNA-damage–agent treatment. But these cellular defects can be compensated by wild-type UBE2T overexpression. As one of E2 enzymes for interaction with FANCL, the interface of RING domain of FANCL binding to UBE2T extends longer hydrophobic surface to Tyr311 than other E3 enzymes, and only UBE2T has a specific Arg60 which has the positive charge to form a salt bridge with FANCL[35]. With

this unique E3-E2 selection, FANCD2 can only be mono- but not poly-ubiquitinated in response to DNA damage response.

Genomic stability maintenance of FANCD2

The similar sensitivity to DNA crosslinking damage revealed from FA cells and yeast rad6-null cells (Rad6−/−) prompted us to explore the potential relationship between the FA and Human Homologs of yeast Rad 6 (HHR6) pathways, in which HHR6-hRad18 activates PCNA, in turn, regulating translesion DNA polymerases including pol ŋ[36]. Now, it is understood that HHR6 and hRad18 (a HHR6 partner), can regulate FANCD2 monoubiquitination[37–39], which bridges the FA and HHR6 pathways in maintaining genome integrity[28, 36]. Moreover, monoubiquitinated FANCD2 can modulate the activity of translesion DNA synthesis through binding to pol ŋ at the regions that have been long known for interacting with PCNA[40, 41]. Importantly, we found that the interaction of pol ŋ with FANCD2 occurs earlier than that with PCNA in response to DNA damage. We also found the similar MMC sensitivity between cells transfected with either wtFANCD2 or histone-fused pol ŋ[42], suggesting that monoubiquitinated FANCD2 may play an anchor role similar to histone's, binding to DNA in the regulation of pol ŋ function. Clearly, in the early response to DNA damage, FANCD2 plays an important role in the recruitment of DNA translesion synthesis enzyme, pol ŋ, to the DNA damage sites for repair[42].

Although monoubiquitination of FANCD2 is essential for FA pathway's activation and the downstream multistep complex recruitment (BRCA-related FA proteins), one recent study reported that this modification is not required for DNA repair. The complex of FANCD2, RAD51C and RAD18 can also support PCNA monoubiquitination and translesion synthesis in a FANCD2 monoubiquitination independent manner upon hydroxyurea treatment but not other DNA damage agents[43], suggesting an unorthodox function of FANCD2 in response to different types of DNA damage.

Besides FANCD2's roles in DNA damage, those in DNA replication appeared to be much less explored. During DNA replication, the entirety of cellular DNA must be faithfully duplicated to maintain genome stability and protect cells from neoplastic transformation. We found that, in normally cycling cells, the basal level of FANCD2 monoubiquitination is required to work with replication initiators for the maintenance of a sufficient number of DNA replication origins to fire in time[44]. The loss of the basal level of monoubiquitinated FANCD2, e.g. the loss of this propitious and steric check before the origin firing in normally growing, non-malignant cells can lead to a slow rate of replication origin firing, chromosomal abnormality, aging and cancer, demonstrated in FA. This finding provides a novel understanding of how FANCD2 functions under normal conditions of cell cycle to maintain genome stability, as well as resulting implications in the strategic improvement for the fight against human cancer. Taken together, FANCD2-centered FA signaling pathway plays a crucial role in the maintenance of genomic stability under both stress and non-stress conditions.

Gain-of-function of impaired FA pathway in human cancer

It is generally believed that FA genes lose their tumor suppressor roles as a consequence of encoded abnormal proteins. We discovered that ΔNP63 was not upregulated in FANCD2 null cells nor in wild type FANCD2-containing cells, instead, upregulated only in FANCD2-inactivated cells[45]. Further mechanistic studies indicate that this is, at least partly, resulting from the directly binding to the ΔNP63 promoter region by inactivated FANCD2 /non-monoubiquitinated FANCD2. In general, inactivated FANCD2 loses its roles in DNA damage repair and DNA replication, which is not indicative of the up-regulation of any genes. It is very exciting that inactivated FANCD2 was found to possess the feature of "Gain of Function". Therefore, the tumorigenicity resulting from impaired FA signaling / inactivated-FANCD2 can be attributed to the gain-of-function, adding a novel layer of complexity in our understanding of the FA tumor-suppressor signaling pathway.

FA pathway-targeted agents in cancer therapy

A considerable cases of cancers arise along with an abnormal FA pathway[24], but a certain percentage of cancer cases with a proficient FA pathway, which conceptually provides a tumor-killing barrier to chemo- and radiotherapy, given its capability in DNA damage repair/ maintenance of genome stability. Thus, inhibition of this pathway may sensitize the tumor cells to DNA damage caused by chemo- or radio-therapies. Besides FAVL compromising the FA pathway[30, 31], some small molecular drugs were also reported recently to reduce the activity of the FA pathway. For instances, PJ34[46], celastrol[47], mTOR kinase inhibitor[48], Nedd8 conjugation system inhibitor[49], DDN[50], phenylbutyrate[51] and monoketone analogs of curcumin[52] are all against FANCD2 monoubiquitination. Mitoxantrone can promotes the activity of USP11[53] and inhibit FANCF[54], and both also compromise FANCD2 monoubiquitination. Further, bortezomib can interfere with FA/BRCA1 focus formation[55] and thus sensitize tumor cells. From these recent studies, many chemical substances developed are aimed at FANCD2 monoubiquitination as a tumor target.

Perspective

The suggestion that the FA pathway is associated with neoplasm in general population was brought up for more than 40 years[56], and it only recently emerged to be an intensive field of cancer research upon our studies and many of others[1, 5, 9–12, 14–17, 30, 31]. The deficient FA pathway promotes the tumorigenesis by not only facilitating genome instability but also the gain of new roles in the induction of additional oncogenic factors to promote tumor cell growth. In contrast, the normal FA pathway protecting tumor cells from the DNA-damage therapy needs to be suppressed. The abundant function of FANCD2 and other FA genes are under intensively studied. Those studies give a rise of more questions on the roles of the downstream FA protein-associated complexes in facilitating DNA repair and potentially novel effects on tumor suppression and cancer treatment. The protein structures and functional domains of these FA protein associated complexes need to be clarified for the principle of a unique platform proposed /suggested widely to support DNA repair. Moreover, the molecular regulatory network of the FA pathway need to be elucidated for the

basis of dynamical responses to DNA damage[57] or during DNA replication[58] in conjunction with proliferation detention[59], inflammatory reaction[60] and/or apoptosis[61]. Finally, the genetic and epigenetic profiles of FA genes in population for hotspot motifs seemingly need to be completely annotated in the hope of aiding the early cancer diagnosis, and its treatment and prognosis. We are facing a long journey to unveil the complexity of the FA signaling pathway in oncology.

Acknowledgements

We thank Drs. Panneerselvam Jayabal, Chi Ma, and Bing Han (lab members) for the helpful discussion. The related work is partly supported by NIH grants R01CA136532 and R01 CA188251 to PF.

References

1. Taniguchi T, D'Andrea AD. Molecular pathogenesis of Fanconi anemia: recent progress. Blood. 2006; 107:4223–4233. [PubMed: 16493006]
2. Fei P, Yin J, Wang W. New advances in the DNA damage response network of Fanconi anemia and BRCA proteins. FAAP95 replaces BRCA2 as the true FANCB protein. Cell Cycle. 2005; 4:80–86. [PubMed: 15611632]
3. Bagby GC Jr. Genetic basis of Fanconi anemia. Curr Opin Hematol. 2003; 10:68–76. [PubMed: 12483114]
4. Huang TT, D'Andrea AD. Regulation of DNA repair by ubiquitylation. Nat Rev Mol Cell Biol. 2006; 7:323–334. [PubMed: 16633336]
5. Huang TT, Nijman SM, Mirchandani KD, Galardy PJ, Cohn MA, Haas W, et al. Regulation of monoubiquitinated PCNA by DUB autocleavage. Nat Cell Biol. 2006; 8:339–347. [PubMed: 16531995]
6. Pickering A, Zhang J, Panneerselvam J, Fei P. Advances in the understanding of the Fanconi anemia tumor suppressor pathway. Cancer Biol Ther. 2013; 14:1089–1091. [PubMed: 24025411]
7. Sala-Trepat M, Rouillard D, Escarceller M, Laquerbe A, Moustacchi E, Papadopoulo D. Arrest of S-phase progression is impaired in Fanconi anemia cells. Exp Cell Res. 2000; 260:208–215. [PubMed: 11035915]
8. Grompe M. FANCL, as in ligase. Nat Genet. 2003; 35:113–114.
9. Hahn SA, Greenhalf B, Ellis I, Sina-Frey M, Rieder H, Korte B, et al. BRCA2 germline mutations in familial pancreatic carcinoma. J Natl Cancer Inst. 2003; 95:214–221. [PubMed: 12569143]
10. Reid SSD, Hanenberg H, Barker K, Hanks S, Kalb R, Neveling K, Kelly P, Seal S, Freund M, Wurm M, Batish SD, Lach FP, Yetgin S, Neitzel H, Ariffin H, Tischkowitz M, Mathew CG, Auerbach AD, Rahman N. Biallelic mutations in PALB2 cause Fanconi anemia subtype FA-N and predispose to childhood cancer. Nat Genet. 2007; 39:162–164. [PubMed: 17200671]
11. Roest HP, Baarends WM, de Wit J, van Klaveren JW, Wassenaar E, Hoogerbrugge JW, et al. The ubiquitin-conjugating DNA repair enzyme HR6A is a maternal factor essential for early embryonic development in mice. Mol Cell Biol. 2004; 24:5485–5495. [PubMed: 15169909]
12. Xia BDJ, Ameziane N, de Vries Y, Rooimans MA, Sheng Q, Pals G, Errami A, Gluckman E, Llera J, Wang W, Livingston DM, Joenje H, de Winter JP. Fanconi anemia is associated with a defect in the BRCA2 partner PALB2. Nat Genet. 2007; 39:159–161. [PubMed: 17200672]
13. Wang AT, Smogorzewska A. SnapShot: Fanconi anemia and associated proteins. Cell. 2015; 160:354–354. e351. [PubMed: 25594185]
14. Meetei AR, Medhurst AL, Ling C, Xue Y, Singh TR, Bier P, et al. A human ortholog of archaeal DNA repair protein Hef is defective in Fanconi anemia complementation group M. Nat Genet. 2005; 37:958–963. [PubMed: 16116422]
15. Wang W. Emergence of a DNA-damage response network consisting of Fanconi anaemia and BRCA proteins. Nat Rev Genet. 2007; 8:735–748. [PubMed: 17768402]

16. Deans AJ, West SC. DNA interstrand crosslink repair and cancer. Nat Rev Cancer. 2011; 11:467–480. [PubMed: 21701511]
17. Bogliolo M, Schuster B, Stoepker C, Derkunt B, Su Y, Raams A, et al. Mutations in ERCC4, encoding the DNA-repair endonuclease XPF, cause Fanconi anemia. Am J Hum Genet. 2013; 92:800–806. [PubMed: 23623386]
18. Sawyer SL, Tian L, Kahkonen M, Schwartzentruber J, Kircher M, Majewski J, et al. Biallelic mutations in BRCA1 cause a new Fanconi anemia subtype. Cancer Discov. 2015; 5:135–142. [PubMed: 25472942]
19. Timmers C, Taniguchi T, Hejna J, Reifsteck C, Lucas L, Bruun D, et al. Positional cloning of a novel Fanconi anemia gene, FANCD2. Mol Cell. 2001; 7:241–248. [PubMed: 11239453]
20. Ahlborn LB, Steffensen AY, Jonson L, Djursby M, Nielsen FC, Gerdes AM, et al. Identification of a breast cancer family double heterozygote for RAD51C and BRCA2 gene mutations. Fam Cancer. 2015; 14:129–133. [PubMed: 25154786]
21. Kohlhase S, Bogdanova NV, Schurmann P, Bermisheva M, Khusnutdinova E, Antonenkova N, et al. Mutation analysis of the ERCC4/FANCQ gene in hereditary breast cancer. PLoS One. 2014; 9:e85334. [PubMed: 24465539]
22. Smetsers S, Muter J, Bristow C, Patel L, Chandler K, Bonney D, et al. Heterozygote FANCD2 mutations associated with childhood T Cell ALL and testicular seminoma. Fam Cancer. 2012; 11:661–665. [PubMed: 22829014]
23. Akbari MR, Malekzadeh R, Lepage P, Roquis D, Sadjadi AR, Aghcheli K, et al. Mutations in Fanconi anemia genes and the risk of esophageal cancer. Hum Genet. 2011; 129:573–582. [PubMed: 21279724]
24. Shen Y, Lee YH, Panneerselvam J, Zhang J, Loo LW, Fei P. Mutated Fanconi anemia pathway in non-Fanconi anemia cancers. Oncotarget. 2015
25. Moldovan GL, D'Andrea AD. How the fanconi anemia pathway guards the genome. Annu Rev Genet. 2009; 43:223–249. [PubMed: 19686080]
26. Garcia-Higuera I, Taniguchi T, Ganesan S, Meyn MS, Timmers C, Hejna J, et al. Interaction of the Fanconi anemia proteins and BRCA1 in a common pathway. Mol Cell. 2001; 7:249–262. [PubMed: 11239454]
27. Smogorzewska A, Matsuoka S, Vinciguerra P, McDonald ER 3rd, Hurov KE, Luo J, et al. Identification of the FANCI protein, a monoubiquitinated FANCD2 paralog required for DNA repair. Cell. 2007; 129:289–301. [PubMed: 17412408]
28. Pickering A, Panneerselvam J, Zhang J, Zheng J, Zhang Y, Fei P. In vitro FANCD2 monoubiquitination by HHR6 and hRad18. Cell Cycle. 2013; 12:3448–3449. [PubMed: 24036990]
29. Zhang J, Wang X, Lin CJ, Couch FJ, Fei P. Altered expression of FANCL confers mitomycin C sensitivity in Calu-6 lung cancer cells. Cancer Biol Ther. 2006; 5:1632–1636. [PubMed: 17106252]
30. Zhang J, Zhao D, Park HK, Wang H, Dyer RB, Liu W, et al. FAVL elevation in human tumors disrupts Fanconi anemia pathway signaling and promotes genomic instability and tumor growth. J Clin Invest. 2010; 120:1524–1534. [PubMed: 20407210]
31. Panneerselvam J, Park HK, Zhang J, Dudimah FD, Zhang P, Wang H, et al. FAVL impairment of the Fanconi anemia pathway promotes the development of human bladder cancer. Cell Cycle. 2012; 11:2947–2955. [PubMed: 22828653]
32. Rickman KA, Lach FP, Abhyankar A, Donovan FX, Sanborn EM, Kennedy JA, et al. Deficiency of UBE2T, the E2 Ubiquitin Ligase Necessary for FANCD2 and FANCI Ubiquitination, Causes FA-T Subtype of Fanconi Anemia. Cell Rep. 2015; 12:35–41. [PubMed: 26119737]
33. Hira A, Yoshida K, Sato K, Okuno Y, Shiraishi Y, Chiba K, et al. Mutations in the Gene Encoding the E2 Conjugating Enzyme UBE2T Cause Fanconi Anemia. Am J Hum Genet. 2015; 96:1001–1007. [PubMed: 26046368]
34. Virts EL, Jankowska A, Mackay C, Glaas MF, Wiek C, Kelich SL, et al. AluY-mediated germline deletion, duplication and somatic stem cell reversion in UBE2T defines a new subtype of Fanconi anemia. Hum Mol Genet. 2015; 24:5093–5108. [PubMed: 26085575]

35. Hodson C, Purkiss A, Miles JA, Walden H. Structure of the human FANCL RING-Ube2T complex reveals determinants of cognate E3-E2 selection. Structure. 2014; 22:337–344. [PubMed: 24389026]
36. Zhang J, Zhao D, Wang H, Lin CJ, Fei P. FANCD2 monoubiquitination provides a link between the HHR6 and FA-BRCA pathways. Cell cycle. 2008; 7:407–413. [PubMed: 18277096]
37. Park HK, Wang H, Zhang J, Datta S, Fei P. Convergence of Rad6/Rad18 and Fanconi anemia tumor suppressor pathways upon DNA damage. PloS one. 2010; 5:e13313. [PubMed: 20967207]
38. Geng L, Huntoon CJ, Karnitz LM. RAD18-mediated ubiquitination of PCNA activates the Fanconi anemia DNA repair network. J Cell Biol. 2010; 191:249–257. [PubMed: 20937699]
39. Song IY, Palle K, Gurkar A, Tateishi S, Kupfer GM, Vaziri C. Rad18-mediated translesion synthesis of bulky DNA adducts is coupled to activation of the Fanconi anemia DNA repair pathway. J Biol Chem. 2010; 285:31525–31536. [PubMed: 20675655]
40. Bienko M, Green CM, Crosetto N, Rudolf F, Zapart G, Coull B, et al. Ubiquitin-binding domains in Y-family polymerases regulate translesion synthesis. Science. 2005; 310:1821–1824. [PubMed: 16357261]
41. Kannouche PL, Wing J, Lehmann AR. Interaction of human DNA polymerase eta with monoubiquitinated PCNA: a possible mechanism for the polymerase switch in response to DNA damage. Mol Cell. 2004; 14:491–500. [PubMed: 15149598]
42. Fu D, Dudimah FD, Zhang J, Pickering A, Paneerselvam J, Palrasu M, et al. Recruitment of DNA polymerase eta by FANCD2 in the early response to DNA damage. Cell cycle. 2013; 12:803–809. [PubMed: 23388460]
43. Chen X, Bosques L, Sung P, Kupfer GM. A novel role for non-ubiquitinated FANCD2 in response to hydroxyurea-induced DNA damage. Oncogene. 2015
44. Panneerselvam J, Pickering A, Han B, Li L, Zheng J, Zhang J, et al. Basal level of FANCD2 monoubiquitination is required for the maintenance of a sufficient number of licensed-replication origins to fire at a normal rate. Oncotarget. 2014; 5:1326–1337. [PubMed: 24658369]
45. Panneerselvam J, Pickering A, Zhang J, Wang H, Tian H, Zheng J, et al. A hidden role of the inactivated FANCD2: upregulating DeltaNp63. Oncotarget. 2013; 4:1416–1426. [PubMed: 23965832]
46. Xiong T, Chen X, Wei H, Xiao H. Influence of PJ34 on the genotoxicity induced by melphalan in human multiple myeloma cells. Arch Med Sci. 2015; 11:301–306. [PubMed: 25995744]
47. Wang GZ, Liu YQ, Cheng X, Zhou GB. Celastrol induces proteasomal degradation of FANCD2 to sensitize lung cancer cells to DNA crosslinking agents. Cancer Sci. 2015; 106:902–908. [PubMed: 25891850]
48. Guo F, Li J, Zhang S, Du W, Amarachintha S, Sipple J, et al. mTOR kinase inhibitor sensitizes T-cell lymphoblastic leukemia for chemotherapy-induced DNA damage via suppressing FANCD2 expression. Leukemia. 2014; 28:203–206. [PubMed: 23852546]
49. Kee Y, Huang M, Chang S, Moreau LA, Park E, Smith PG, et al. Inhibition of the Nedd8 system sensitizes cells to DNA interstrand cross-linking agents. Mol Cancer Res. 2012; 10:369–377. [PubMed: 22219386]
50. Landais I, Sobeck A, Stone S, LaChapelle A, Hoatlin ME. A novel cell-free screen identifies a potent inhibitor of the Fanconi anemia pathway. Int J Cancer. 2009; 124:783–792. [PubMed: 19048618]
51. Burkitt K, Ljungman M. Phenylbutyrate interferes with the Fanconi anemia and BRCA pathway and sensitizes head and neck cancer cells to cisplatin. Mol Cancer. 2008; 7:24. [PubMed: 18325101]
52. Landais I, Hiddingh S, McCarroll M, Yang C, Sun A, Turker MS, et al. Monoketone analogs of curcumin, a new class of Fanconi anemia pathway inhibitors. Mol Cancer. 2009; 8:133. [PubMed: 20043851]
53. Burkhart RA, Peng Y, Norris ZA, Tholey RM, Talbott VA, Liang Q, et al. Mitoxantrone targets human ubiquitin-specific peptidase 11 (USP11) and is a potent inhibitor of pancreatic cancer cell survival. Mol Cancer Res. 2013; 11:901–911. [PubMed: 23696131]

54. Li Y, Zhao L, Sun H, Yu J, Li N, Liang J, et al. Gene silencing of FANCF potentiates the sensitivity to mitoxantrone through activation of JNK and p38 signal pathways in breast cancer cells. PLoS One. 2012; 7:e44254. [PubMed: 22952942]

55. Jacquemont C, Simon JA, D'Andrea AD, Taniguchi T. Non-specific chemical inhibition of the Fanconi anemia pathway sensitizes cancer cells to cisplatin. Mol Cancer. 2012; 11:26. [PubMed: 22537224]

56. Swift M. Fanconi's anaemia in the genetics of neoplasia. Nature. 1971; 230:370–373. [PubMed: 4927726]

57. Du W, Rani R, Sipple J, Schick J, Myers KC, Mehta P, et al. The FA pathway counteracts oxidative stress through selective protection of antioxidant defense gene promoters. Blood. 2012; 119:4142–4151. [PubMed: 22408259]

58. Kato Y, Alavattam KG, Sin HS, Meetei AR, Pang Q, Andreassen PR, et al. FANCB is essential in the male germline and regulates H3K9 methylation on the sex chromosomes during meiosis. Hum Mol Genet. 2015; 24:5234–5249. [PubMed: 26123487]

59. Li X, Li J, Wilson A, Sipple J, Schick J, Pang Q. Fancd2 is required for nuclear retention of Foxo3a in hematopoietic stem cell maintenance. J Biol Chem. 2015; 290:2715–2727. [PubMed: 25505262]

60. Kaschutnig P, Bogeska R, Walter D, Lier A, Huntscha S, Milsom MD. The Fanconi anemia pathway is required for efficient repair of stress-induced DNA damage in haematopoietic stem cells. Cell Cycle. 2015; 14:2734–2742. [PubMed: 26178207]

61. Sakai W, Sugasawa K. FANCD2 is a target for caspase 3 during DNA damage-induced apoptosis. FEBS Lett. 2014; 588:3778–3785. [PubMed: 25176410]