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Review

Quick glance at Fanconi anemia and BRCA2/FANCD1

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Abstract: Fanconi anemia (FA) is a rare genetic disorder characterized by multiple congenital malformations, progressive bone marrow failure, and susceptibility to cancer. The FA-D1 subtype is associated with biallelic mutations in the breast cancer 2 genes also known as FANCD1. Patients with this mutation display severe disease phenotype. In addition, different types of cancer other than breast cancer are associated with this mutation, such as leukemia, solid tumors of the central nervous system, etc. In this review, we have surveyed the literature on FA, FA genes, their biological roles, and specifically discussed the current information available on the FA-D1 disease subtype. The observations show that the timing of biallelic loss of BRCA2 can establish the specific cancer spectrum. The knowledge about effects of the FANCD1/BRCA2 mutation on FA and cancer pathogenesis can be used for further understanding the FA-D1 subtype of the disease.

Keywords: Fanconi anemia; interstrand crosslink; ubiquitylation; FANCD1; BRCA2

1. Introduction

Fanconi anemia (FA) is a pathologically diverse and recessive autosomal inherited rare genetic disorder that occurs in one in 130,000 births and is common among Ashkenazi Jews and South Africans [1]. It is caused by mutations in a cluster of proteins that perform DNA repair, especially those of covalent interstrand crosslinks (ICLs), via homologous recombination. FA culminates in bone marrow failure (BMF) in 90% of the affected individuals and leads to the development of various types of cancer, particularly myelogenous leukemia; gynecological squamous cell carcinoma; tumors in the liver, brain, skin, and kidney; esophageal carcinoma; and aggressive head and neck squamous cell carcinoma [2–4]. Approximately, 60–75% of the affected people have congenital defects, short stature, skin hyperpigmentation, missing radii, and abnormal thumb, head, eyes, kidneys, and ears, and developmental disabilities, and 75% people exhibit endocrine disorders of varying severity. The first

sign of a hematological problem is usually petechiae and bruises, with later onset of pale appearance, tiredness, and infections.

Several patients develop BMF sometime during the course of the disease, but the onset of pancytopenia is correlated with the probability of FA. However, in some patients, the condition remains undiagnosed until the development of myelodysplastic syndromes/acute myeloid leukemia (MDS-AML). Patients with FA exhibit elevated levels of serum alpha-fetoproteins, fetal hemoglobin (HbF), and macrocytosis, although these cannot exclusively predict FA [5]. FA can be diagnosed in patients of age 0–48 years, and nearly 25–40% patients with FA appear healthy [6].

The commonly available treatment strategies for BMF involve the use of androgens and hematopoietic growth factors; however, cases where patients have become refractory to these treatments have been reported. In such cases, hematopoietic stem cell transplantation is the treatment of choice depending on the availability of a donor. For solid tumors in patients with FA, surgery is the preferred mode of treatment than radiotherapy and chemotherapy due to the possibility of severe side effects [7].

2. Genes involved in FA

The list of mutations in genes associated with FA has increased ever since the discovery of the first FA gene, FANCC, over 25 years ago. There are over 22 known FA complementation groups, such as FANC-A, B, C, D1, D2, E, F, G, I, J, L, M, N, O, P, Q, R, S, T, U, V, and W [8]. All the proteins associated with FA pathway and their individual functions have been depicted in the Table 1 [9].

Table 1. Proteins in FA pathway and their individual roles [9].

FA Proteins	Involved in DNA damage	Involved in other cellular processes
FANCA		CD40 signaling pathway; cell proliferation; inflammatory response; T cell differentiation; Sequence-specific DNA binding transcription factor activity
FANCB	DNA damage repair (not entirely dependent on the FA core complex)	
FANCC	TP53 Regulation of DNA Repair Genes	Generic transcription pathway; Gene expression; Diabetes
FANCD1	DNA damage repair, (not entirely dependent on the monoubiquitinated D2/I)	Cell cycle regulation; meiotic recombination; Presynaptic phase of homologous DNA pairing and strand exchange; Resolution of D-loop structures

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FA Proteins	Involved in DNA damage	Involved in other cellular processes
FANCD2	The HHR6 signaling pathway; The ATM signaling pathway; DNA damage repair; TP53 regulation of DNA Repair Genes; MiRNA regulation of DNA damage response	Replication: Replication-origin firing, Stalled replication forks; Mitochondria function; gene expression;
FANCE/F/G	DNA damage repair (not entirely depending on the FA core complex)	
FANCI	The ATR signaling pathway; TP53 regulation of DNA Repair Genes; DNA damage repair	Gene expression
FANCJ	DNA damage repair (not entirely dependent on the monoubiquitinated D2/I); G2/M DNA damage checkpoint	Cell cycle regulation; Cytosolic iron-sulfur cluster assembly; P53 activity; Presynaptic phase of homologous DNA pairing and strand exchange; Resolution of D-loop structures
FANCL	DNA damage repair (not entirely dependent on the FA core complex)	Ubiquitin mediated proteolysis
FANCM	ATR regulator, or a major sensor of the DDR	Stalled replication forks
FANCN	DNA damage repair (HR) (not entirely dependent on monoubiquitinated FANCD2)	Resolution of D-loop structures; Homologous DNA Pairing and Strand Exchange
FANCO	DNA damage repair (not entirely dependent on monoubiquitinated FANCD2)	Meiosis; Resolution of D-loop structures; Megakaryocyte development and platelet production; Cell cycle
FANCP	DNA damage repair (not entirely dependent on monoubiquitinated FANCD2/I)	Resolution of D-loop structures
FANCQ	DNA damage repair (DSB, NER) (not entirely dependent on monoubiquitinated FANCD2)	Transcription
FANCR	DNA damage repair (HR) (not entirely dependent on monoubiquitinated FANCD2/I); ATM signaling	Cell cycle; Meiosis; Rac1/Pak1/p38/MMP-2 pathway

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FA Proteins	Involved in DNA damage	Involved in other cellular processes
FANCS	DNA damage repair (HR) (not entirely dependent on monoubiquitinated FANCD2/I); ATM signaling	Transcription (ATF-2, E2F, FOXA1 transcription factor networks); Androgen receptor signaling pathway; Aurora A signaling; Cell Cycle Checkpoints; Deubiquitinating;
FANCT	DNA damage repair (not entirely dependent on monoubiquitinated FANCD2/I);	Post-translational protein modification
FANCU	DNA damage repair (not entirely dependent on monoubiquitinated FANCD2/I)	Resolution of D-loop structures; Presynaptic phase of homologous DNA pairing and strand exchange
FANCV	TLS performed by POL1, POLK, REV1 or Zeta; post replication repair (not entirely dependent on monoubiquitinated FANCD2/I)	Cell cycle regulation; Shigellosis; Oocyte meiosis; Endoderm Differentiation
FANCW	Ubiquitination of RPA (not entirely for the activation of the FA pathway)	Ubiquitination; Mediation of p53 ubiquitination for its stability

Moreover, mutations in FANCO, RAD51 (FANCR), and FANCS have been implicated in a FA-like syndrome in which patient cells are hypersensitive to ICL-inducing drugs, but the disease is not characterized with all the clinical features classically observed in FA. Among the bona fide FA genes, FANCA, FANCC, and FANCG are the most frequently inactivated by biallelic mutations linked to the hereditary disorder [10,11]. Importantly, monoallelic mutations in certain FA genes, including FANCD1 (BRCA2), FANCS (BRCA1), FANCN (PALB2), FANCM, FANCJ (BRIP1), and FANCO (RAD51C), which are believed to operate downstream in the pathway and are implicated in homologous recombination, are associated with sporadic breast and ovarian cancer [11,12]. With the identification of several FA genes, the pathway for repair of ICLs has become more complex and is now believed to involve nucleotide excision repair, base excision repair, double strand break repair, and mismatch repair. Although ICL repair occurs mostly in replicating cells, studies have also associated it with non-replicative repair, such as in cells treated with DNA crosslinking agents. ICL repair is critical as it affects DNA unwinding for basic life processes such as transcription and replication.

FA pathway/signaling is crucial for DNA damage response (DDR), which further results in DNA ICL. However, it has been reported that genes and proteins, especially FANCC, of the FA pathway perform additional cytoprotective role. FANCC provides protection against proinflammatory cytokine-induced cell death. This role is associated with FANCC and its various biochemical interactions [13]. One study suggested that patients with FA carrying endogenously expressed *FANCC* mutant c.67delG exhibited a clinical course that was milder than patients with null mutations in *FANCC* [14]. FA cells are hypersensitive to oxidative stress, radio/chemotherapeutic agents, and DNA crosslinking agents, such as mitomycin, and exhibit cell cycle abnormalities [15]. Thus, FA phenotypes may require stressors to initiate the disease phenotype [16]. Thus, bone marrow transplant should be performed

with extreme care so as not to induce any oxidative stress, especially via radio/chemotherapeutic agents, which may otherwise lead to BMF.

3. FA genes and ICL repair

FANCA, FANCB, FANCC, FANCE, FANCF, FANCG, FANCL, and FANCM form a core complex, which monoubiquitylates FANCD2 and FANCI [17–20]. The monoubiquitylated complex interacts with the endo/exonuclease FAN1 (FA associated nuclease 1) [20–24]. However, FA patients with mutations in FAN1 are not known till date. FANCD1/BRCA2 and BRCA2-interacting protein FANCN/PALB2, essential components of homologous recombination repair, act downstream in this pathway along with the helicase FANCJ /BRIP1/BACH1 [25–31]. The interaction of FANCJ with BRCA1 is dispensable for the FA pathway. Interestingly, although BRCA1 depletion sensitizes cells to crosslink damage, individuals with biallelic BRCA1 mutations have not been reported so far. Multiple proteins, including the nucleases XPF, MUS81, and SLX1, interact with FANCP/SLX4, the latest addition to the family of FA proteins, which acts as a protein scaffold [32–37]. XPF and MUS81 are involved in crosslink repair, and the SLX4-SLX1 interaction is responsible for Holliday junction resolution activity in vitro. However, which activity of SLX4 is essential for crosslink repair is currently unclear [38,39]. Overall, it is clear that mutations in FA proteins, which perturb ICL resolution, are important for FA pathogenesis.

4. FANCD1/BRCA2

BRCA2, a human tumor suppressor, is also known as FANCD1, indicating its associations with the FA complex (discussed above) [40,41]. It is normally expressed in breast tissues and is involved in the repair of DNA damage as described in the previous section. BRCA2 also prevents nucleolytic degradation of stalled forks during DNA replication [42]. Thus, BRCA2 is critical for maintaining genome stability and preventing deleterious genomic rearrangements, which may lead to cancer. High penetrance mutations in BRCA2/FANCD1 lead to loss of its tumor suppressive character and increase the chances of developing breast cancer [43].

Several mutations, usually small indels, have been identified in BRCA2, many of which increase the risk of cancer. These mutations lead to the synthesis of an abnormal product that does not function properly. In their analysis of the severity of BRCA2 mutations in 27 cases with breast cancer, Alter et al. (2007) showed that 20 mutations were frameshifts or truncations, three involved splice sites, five were missense variants of unknown severity, and two were benign polymorphisms [44]. Monoallelic germline mutations in BRCA2 increase the susceptibility for breast/ovarian cancer, whereas biallelic germ line mutations lead to the development of FA-D1 in patients. Indeed, among the known FA genes, only BRCA2/FANCD1 plays a major role in the development of high-risk breast cancer [45]. BRCA2-associated FA-D1 subtype accounts for nearly 3% of all FA cases, which, in comparison with other subtypes, results in more severe form of the phenotype, increases the frequency of leukemia and other tumors, as well as early onset of symptoms [44,46]. Parents of patients with FA are heterozygous for the condition, and therefore are at a high risk of early-onset breast/ovarian cancer [47]. Furthermore, in heterozygous patients, loss of the second wild type BRCA2 allele leads to biallelic extinction of BRCA2, and subsequent exposure to DNA cross-linkers often result in chromosome breakage, resulting in tri-radial chromosomes, which are characteristic of FA cells [48].

Thus, FA and breast cancer are interlinked and share common functions in the DNA repair mechanism [49]. Children with biallelic mutation in BRCA2 show spontaneous chromosomal instability and develop solid tumors of childhood such as Wilm's tumor and medulloblastoma [50].

Individuals with heterozygous mutations in BRCA2/FANCD1 are also at increased risk of developing pancreatic cancer. Hahn et al. (2003) showed that frameshift mutations in BRCA2/FANCD1were associated with 19% cases with history of hereditary pancreatic cancer [51]. Similarly, other cancers, such as prostate cancer, gastric cancer, and melanoma, have also been associated with heterozygous mutations in BRCA2/FANCD1 [52]. A recent study showed that colorectal cancer (CRC) can also be associated with biallelicBRCA2 mutations (a frameshift alteration (c. 1845_1846delCT, p. Asn615Lysfs*6) and a missense mutation (c. 7802A > G, p. Tyr2601Cys)) in families with cases of CRC, although CRC driver genes were not involved and the cardinal clinical symptoms of FA were not observed. This indicated that the presence of these mutations should be screened even in the absence of typical FA symptoms [53]. The biallelic p. Lys3326X mutation in BRCA2 was present in 27 of 746 ESCC cases and in 16 of 1,373 controls in a study on mutations in FA genes in Turkmen of Iran with esophageal cancer [54].

Recently, biallelic BRCA2 mutation was found to predispose toward glioblastoma multiforme (GBM), with multiple genetic rearrangements [55]. In that study, methylation analysis of GBM from a 3-year-old patient with FA, who harbored biallelic mutation in BRCA2, revealed strong clustering with the K27 mutation subgroup, copy number analysis showed gains of chromosomes 1q, 4q, part of 7q, part of 8q and 17q, with resultant amplifications of MDM4, CDK6, MET, MYC, and PPM1D (WIP1). This study also reported the first germline mutation in BRCA2, c. 8057T > C, resulting in p. Leu2686Pro substitution in the patient. Biallelic BRCA2 mutation has also been reported in two siblings with early age central nervous system embryonal tumor, which is the first reported case of a spinal cord primitive neuroectodermal tumor in BRCA2/FANCD1 kindred [56].

Currently, the precise effect of mutations in some FA gene leading to breast and ovarian cancer remains unclear. While somatic cells with mutations in the DNA repair pathway undergo apoptosis, estrogen might promote the survival of breast and ovarian cells. Estrogen possibly promotes the survival of breast and ovarian cells harboring significant DNA damage, whereas apoptosis may occur in somatic cells with mutations in the DNA repair pathway [57]. In contrast, breast/ovarian cancer infrequently develop in patients with FA. Hypogonadism with decreased levels of estrogen in females with FA might account for this observation. In families carrying BRCA2/FANCD1 mutations, > 40 years marks the peak age for the onset of breast/ovarian cancer among heterozygote carriers, whereas patients with biallelic mutations frequently die from complications of aplastic anemia before 40 years [58]. Altogether, these observations show that the timing of biallelic loss of BRCA2 can establish the specific cancer spectrum [59–65]. Figure 1 provides a schematic representation of FA pathway [66].

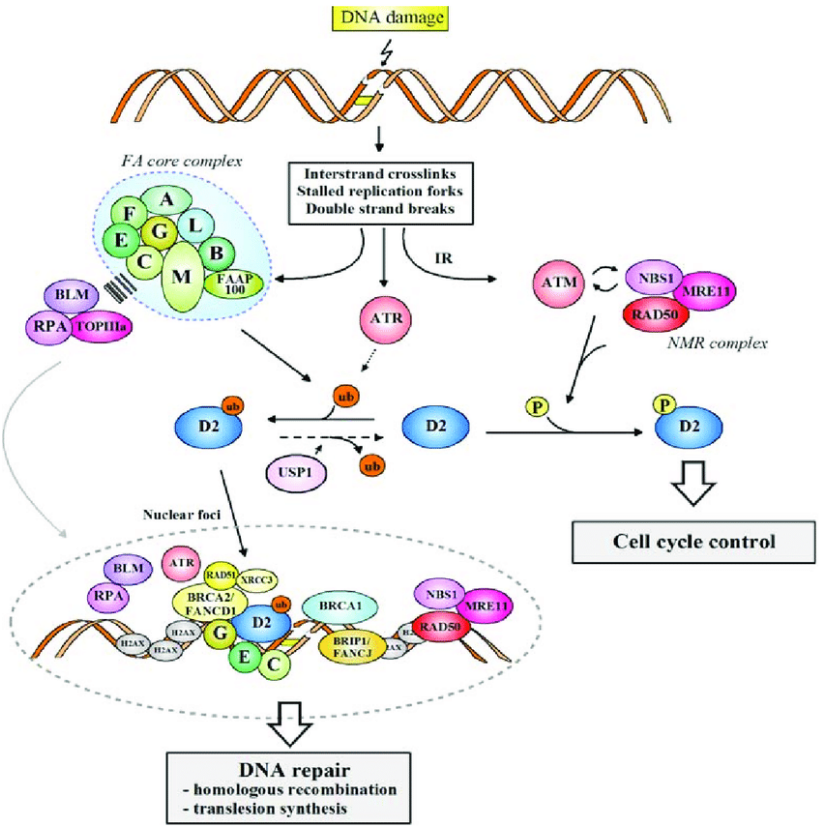

Figure 1. FA pathway at a glance [66].

5. Conclusion

FA is a genetic disorder that predisposes patients to pancytopenia, MDS, and AML. Better understanding of the FA pathway might lead to the development of methods for correcting the perturbed pathway, thereby preventing carcinogenesis in FA patients or those carrying mutations in FA genes. Indeed, the CRISPR/Cas9 technology has already been used to rectify a FANCD1 deletion in a patient-derived fibroblast with the above mutation, providing proof-of-principle that gene editing may be used to rectify FA. As the sensitivity of cancer cells to chemotherapy drugs is affected by defective DNA repair mechanism, mutations in FA genes could help in predicting the success of chemotherapy drugs such as DNA inhibitors, or DNA crosslinking agents (melphalan, mitomycin C, and cisplatin). In this review, we have specifically discussed the effects of the FANCD1/BRCA2 mutation on FA and cancer pathogenesis. The collective knowledge can be used for further understanding the FA-D1 subtype of the disease.

Acknowledgments

None

Conflict of interest

The author declares no conflicts of interest in this paper.

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