Potential role of Fanconi anemia pathway in the pathogenesis of endometrial cancer (Review)

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Abstract. Endometrial cancer (EC) is a common gynecologic malignancy that often exhibits molecular features such as extensive somatic copy number alterations, microsatellite instability and frequent *TP53* mutations, which considerably affect the physical and mental well-being of women. The Fanconi anemia (FA) pathway is a DNA damage repair pathway involving multiple FA genes that play crucial roles in DNA damage repair as well as the maintenance of genome stability. Abnormalities in FA, such as deletions or mutations, may lead to defects in DNA damage repair, resulting in increased genomic instability and/or an abnormal cell cycle, ultimately leading to EC. This comprehensive review provides a systematic summary of EC-related FA genes, elucidates the roles of various FA genes in EC and further speculates on their related mechanisms to facilitate the development of targeted therapies that specifically target key genes, leading to a more accurate and efficient treatment for EC. The present review searched PubMed and Google Scholar for articles published in English up to June 2025 using keywords such as Fanconi anemia pathway, 22 FA genes (*FANCA*, *FANCB*, *FANCC*, *FANCD1/BRCA2*, *FANCD2*, *FANCE*, *FANCF*, *FANCG*, *FANCI*, *FANCJ/BRIP1*, *FANCL*, *FANCM*, *FANCN/PALB2*, *FANCO/RAD51C*, *FANCP/SLX4*, *FANCQ/XPF*,*FANCR/RAD51*,*FANCS/BRCA1*,*FANCT/UBE2T*, *FANCU/XRCC2*, *FANCV/REV7*, *FANCW/RFWD3*), endometrial cancer (type I: Endometrioid adenocarcinoma; Type II Uterine serous carcinoma, clear-cell carcinoma, carcinosarcoma), somatic copy number alterations, microsatellite instability, TP53 mutations, pathogenesis, genomic instability, target therapy.

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Abbreviations: EC, endometrial cancer; EAC, endometrioid adenocarcinoma; SCNA, somatic copy number alterations; MSI, microsatellite instability; FA, Fanconi anemia; ICL, interstrand cross-linking; DDR, DNA damage response; HR, homologous recombination; ID2, FANCI-FANCD2; TLS, trans lesion synthesis; DSBs, DNA double-strand breaks; LS, Lynch syndrome; UC, uterine cancer; MMR, mismatch repair; A-EMS, atypical endometriosis; TCGA, The Cancer Genome Atlas; WES, whole-exome sequencing; SNP, single nucleotide polymorphism

Key words: cell cycle, DNA damage repair, endometrial cancer, Fanconi anemia, genomic instability

Contents

1. Introduction

Endometrial cancer (EC) is one of the most prevalent gynecological malignancies worldwide (1); its global incidence has increased annually over the past 20 years. Although >50% of women diagnosed with EC are aged 50-69 years, the diagnosis rate in women aged <50 years has shown an increasing trend. Although the overall mortality rate has slightly decreased in recent years, EC remains one of the leading causes of cancer-related deaths among postmenopausal women in a number of countries (2-4). Traditionally, EC has been classified into two main types: Endometrioid (type I)

and non-endometrioid (type II). Type I is a low-grade tumor associated with high estrogen levels, with the histological type of endometrioid adenocarcinoma (EAC) accounting for ~80% of all EC cases. Of the patients, 95% have a good prognosis. By contrast, type II is a highly aggressive, high-grade tumor, including serous carcinoma of the uterus, clear cell carcinoma and carcinosarcoma, with a poor prognosis (5-9). Type II carcinomas and 25% of high-grade type I carcinomas exhibit extensive somatic copy number alterations (SCNA), frequent *TP53* mutations and other molecular manifestations, whereas most type I carcinomas exhibit microsatellite instability (MSI) (10), indicating that genomic instability and cell cycle abnormalities may be closely related to the development of EC.

Normal function and growth of cells depend on the orderly progression of the cell cycle. In both unicellular and multicellular eukaryotes, the cell cycle is regulated by a complex network of regulatory mechanisms (11). In this complex network, genes involved in the DNA damage repair pathway play an important role and abnormalities in these genes may affect endometrial cell genome stability and/or lead to the failure of cell cycle regulation, increased susceptibility to EC and even ultimately trigger EC. The Fanconi anemia (FA) pathway plays a crucial role in DNA interstrand cross-linking (ICL) repair and the maintenance of genomic integrity (12). FA genes participate in DNA damage response (DDR) through the FA and homologous recombination (HR) pathways (13). FA gene deletions or variants may lead to DNA damage repair defects, causing genomic instability such as SCNA and MSI, or cell cycle abnormalities, ultimately leading to the development of EC. The present comprehensive review aimed to summarize the association between FA genes and EC occurrence, explore the potential relationship, open new avenues for future research on EC and FA genes and provide potential insights into the treatment of EC.

2. Mechanisms of FA

FA is rare a chromosomal disorder characterized by genomic instability and an increased susceptibility to cancer caused by mutations in the FA gene. By contrast, the FA pathway, a DNA damage repair pathway involving multiple FA genes, is crucial for normal DNA repair processes and maintenance of genomic stability (14). To date, 22 genes involved in the FA pathway have been identified and can be categorized into upstream, midstream and downstream components. The upstream genes include the lesion recognition gene *FANCM*, FA core complex-related genes (*FANCA*, *FANCB*, *FANCC*, *FANCE*, *FANCF*, *FANCG and FANCL*) and the E2 ubiquitin ligase-related gene *FANCT/UBE2T*. Midstream genes include *FANCD2* and *FANCI*, which form the *FANCI-FANCD2* (ID2) complex. The downstream genes included HR repair-related genes (*FANCD1/BRCA2*, *FANCJ/BRIP1*, *FANCN/PALB2*, *FANCO/RAD51C*, *FANCR/RAD51*, *FANCS/BRCA1*, *FANCU/XRCC2 and FANCW/RFWD3*), nucleolytic incision-related genes (*FANCQ/XPF and FANCP/SLX4*) and trans-lesion synthesis (TLS)-related genes *FANCV/REV7* (15). The entire FA core complex consists of seven FA proteins (FANCA, FANCB, FANCC, FANCE, FANCF, FANCG and FANCL) and FANCA-associated peptides FAAP100, FAAP24 and FAAP20 (16,17). FAAP24 can target FANCM to form the FANCM-FAAP24 complex, recognize ICL and promote the recruitment of the FA core complex to DNA damage sites to participate in DNA damage repair (18). This core complex has E3-ubiquitin ligase activity and is essential for DNA damage repair by mediating mono-ubiquitination of the ID2 complex in response to DNA damage (15). The ID2 complex plays a critical role in the FA pathway and is recruited to the ICL site before FANCD2 mono-ubiquitination, thus participating in pathway activation (19). Additionally, downstream FA genes coordinate the three key DNA repair processes: Nucleolytic incision, TLS and HR, all of which are essential for ICL repair (20). The FA pathway plays a key role in DNA damage repair and participates in DNA damage repair and the maintenance of genome stability by interacting with other DNA repair pathways. Defective DNA repair increases genomic instability, which may lead to cancer development. Several FA genes are closely associated with EC (21). To elucidate the roles of FA genes in EC, the upstream (Table I), midstream (Table II) and downstream genes (Table III) of the EC-associated FA pathway were considered entry points and the underlying mechanisms contributing to EC development and progression were explored.

3. FA genes and EC occurrence

Upstream FA genes and EC

i) FANCE. FANCE encodes a 58 kDa nuclear protein and its products are components of the FA core complex. The integrity of this complex is essential for DNA damage repair and genomic stability (22,23). Using CBioportal data analysis, Salomão *et al* (21) found that the *FANCE* mutation rate in EC was 4.54%. Lynch syndrome (LS) is a common hereditary cancer that is associated with EC. de Angelis de Carvalho *et al* (24) incidentally identified a variant of the *FANCE* gene (c.929dupC; p.Val311Serfs*2-LP) during germline polygenic testing in 14 patients. Zheng *et al* (25) found that *FANCE* expression was markedly lower in EAC than in normal endometrium and that reduced expression was associated with older age and higher tumor grade. By constructing *FANCE*-overexpressing EC cells, we found that *FANCE* overexpression promoted the repair of ICL and double-strand breaks (DSBs) in EC. However, in contrast to the findings of Zheng *et al* (25), Zhou *et al* (26) analyzed the *FANCE* gene in 33 types of cancer, including EC and found that high *FANCE* expression was markedly positively associated with MSI, particularly in EC. This contradiction may be due to interference from different subtypes of EC (EAC compared with mixed subtypes) and the possible biphasic function of *FANCE* in EC. In the early stages, it repairs DNA damage and acts as a tumor suppressor, whereas in the late stages, its continued high expression causes erroneous repair, leading to MSI and acting as a tumor promoter. Zheng *et al* (25) found that *FANCE* is involved in cell cycle regulation. Overexpression of *FANCE* leads to S phase delay and G_2/M phase arrest in EC cells, thereby inhibiting the growth of EC tumors in nude mice, whereas low expression

Table I. Functional evidence of upstream FA gene in EC.

Gene	Function	Experimental evidences	Potential mechanism	EC subtypes
FANCE	FA core complex	Genetic testing (24) Cell model (25)	MSI (26) Cell cycle regulation (25,27)	Type I EC (EAC)
FANCC	FA core complex	Genetic testing (29) Mouse model (33)	DNA replication fork stagnation (30) Cell cycle regulation (31,33)	EC
FANCA	FA core complex	Genetic testing (38-41) Clinical patients (38-41)	MSI (38) MMR (37)	Type I EC

FA, Fanconi anemia; EC, endometrial cancer; MSI, microsatellite instability; MMR, mismatch repair; EAC, endometrioid adenocarcinoma.

Table II. Functional evidence of midstream FA gene in EC.

Gene	Function	Experimental evidences	Potential mechanism	EC subtypes	Clinical significance
FANCD2	ID2 complex	Cell model (43) Clinical patients (9)	MSI (44) Cell cycle regulation (43)	Type I EC Type II EC	Evaluating prognosis
FANCI	ID2 complex	Cancer Genome Atlas (49, 50) Clinical patients (49-51)	Downregulation of TP53 expression (47) SCNA (49,50) HR repair defects (51)	Type II EC (UC)	Evaluating prognosis

FA, Fanconi anemia; EC, endometrial cancer; MSI, microsatellite instability; SCNA, somatic copy number alterations; ID2, FANCI-FANCD2; HR, homologous recombination; UC, uterine cancer.

induces genomic instability and promotes EC development. Furthermore, Lin *et al* (27) found that *FANCE* may participate in regulating squamous cell carcinoma cell cycle through the Wnt/β-catenin signaling pathway, but whether this mechanism applies to EC needs to be further verified in EC models. In summary, abnormal expression or mutation of *FANCE* may lead to EC by affecting DNA damage repair, cell cycle, microsatellite stability and other factors. However, there are still contradictions regarding the direction of action and the molecular mechanisms of this gene in EC. Future studies are needed to distinguish EC subtypes further and to verify their functions and specific molecular mechanisms in different EC subtypes.

ii) FANCC. FANCC is a key component of the FA core complex that promotes two DNA damage repair processes, HR repair and TLS, which are essential for maintaining genomic stability (28). Research has found that the mutation rate of the *FANCC* gene in EC is 5.1 (21). EC is one of the most common uterine cancers (UC). In a study by Heald *et al* (29), four pathogenic or possibly pathogenic germline variants of the *FANCC* gene were identified by genetic testing of 953 patients with UC, indicating that variants in this gene may increase the risk of EC. *FANCC* gene deletion leads to stalling of the DNA replication fork, thereby increasing genomic instability (30), which drives EC development. Additionally, *FANCC* is involved in cell cycle regulation (31). *FANCC* mutations result in DNA damage repair defects, increased spontaneous chromosome breaks and G_2/M phase arrest (28,32). Li *et al* (33) found that *FANCC*-deficient mice exhibited cell cycle abnormalities that promoted the malignant progression of endometrial cells. The *FANCC* gene is associated with multiple FA genes. For example, *FANCC* and *FANCG* jointly participate in the monoubiquitination of *FANCD2* (32). Additionally, FANCC forms a complex with FANCE and FANCF (the FANCC-FANCE-FANCF complex) to regulate meiotic recombination (34). However, this functional synergistic mechanism has not been explored in EC models. Whether the *FANCC* gene has a specific effect on different EC subtypes requires further investigation.

iii) FANCA. As a key component of the FA core complex (13), FANCA plays a crucial role in the repair of DSBs and ICL through the HR repair pathway in the S/G_2 phase of cells, which is essential for maintaining genome stability (35,36). In addition, *FANCA* participates in the mismatch repair (MMR) process by enhancing the interactions between *MSH2* and *MLH1* (37). Salomão *et al* (21) discovered a high mutation rate of *FANCA* in the upstream FA gene in EC, with mutation rates as high as 8.88%. Drusbosky *et al* (38) analyzed genomic data from 1,988 patients, of whom 12% exhibited high levels of MSI and a small number of patients were found to have pathogenic *FANCA* germline mutations. Kral *et al* (39) conducted germline genetic testing on 527 patients, of whom 284 had type I cancer and found that *FANCA* was a candidate susceptibility gene for EC. In addition, Drusbosky *et al* (38) and Liu *et al* (40)

Table III. Functional evidence of downstream FA gene in EC.

Gene	Function	Experimental evidence	Potential mechanism	EC subtypes
FANCN	HR repair	Genetic testing (62) Clinical patients (63-65) Mouse model (67)	SCNA (66) TP53/Cell cycle regulation (67)	Type I EC (EAC)
FANCO	HR repair	Genetic testing (64,71)	HR repair defects (63) Cell cycle regulation (68)	Type II EC (UC)
FANCJ	HR repair	Genetic testing (60,76,78) Clinical patients (71,77) Mouse model (79)	HR repair defects (72) Cell cycle regulation (75) MSI (79)	Type I EC Type II EC
FANCS/ FANCD1	HR repair	Cohort study (84) Genetic testing (77,85,86) Clinical patients (77,85,86)	HR repair defects (77) TP53/ Cell cycle regulation (82,83) MSI (86) SCNA (86)	Type I EC Type II EC (UC)
FANCR	HR repair	Clinical patients (88)	HR repair defects (88)	Type II EC
FANCU	HR repair	Genetic testing (98,99) Clinical patients (98,99)	HR repair defects (96,97) MSI (99)	Type I EC (EAC)
FANCW	HR repair	Genetic testing (21)	HR repair defects (102) Cell cycle regulation (103,104)	EC

FA, Fanconi anemia; EC, endometrial cancer; HR, homologous recombination; SCNA, somatic copy number alterations; MSI, microsatellite instability; EAC, endometrioid adenocarcinoma; UC, uterine cancer.

found that somatic mutations in the *FANCA* gene are also associated with EC. Atypical endometriosis (A-EMS) is associated with endometrial intraepithelial neoplasia. Recently, Wepy *et al* (41) revealed that 25% of 36 patients with A-EMS had concurrent EMS-related tumors, such as ipsilateral endometrioma, serous tumors, or clear cell tumors. A frameshift mutation in the *FANCA* gene (p.I865Kfs*20) was detected by second-generation sequencing in six patients with A-EMS. Although multiple studies (21,38-41) have suggested an association between *FANCA* abnormalities and EC, the specific mechanisms by which *FANCA* mutations contribute to EC remain unclear. According to current research, mutations in this gene may impair DNA damage repair by affecting the FA pathway or MMR, thereby increasing the risk of EC. Future studies should further refine EC subtypes to investigate the role of this gene and its specific mechanisms of action across different EC subtypes.

Midstream FA genes and EC

ID2 ubiquitination-related genes

i) FANCD2. FANCD2 plays a key role in DNA damage repair by interacting with FANCI to form the ID2 complex, which is critical for activating the FA pathway (42). Research has shown that the mutation rate of *FANCD2* in EC is 9.07% (21). In addition, immunohistochemical results show that compared with normal tissue and atypical hyperplasia tissue, the expression level of *FANCD2* is markedly upregulated in type I EC tissue. Knockdown of *FANCD2* can lead to cell cycle arrest in the G_1 phase in EC cell lines, thereby inhibiting their proliferation and migration of EC cells (43). At the same time, Mhawech-Fauceglia *et al* (9) evaluated the expression of various DNA repair proteins in tumor cells from 357 EC patients (of these, 262 cases were type I EC, 76 cases were type II EC and 19 cases were carcinosarcoma) and found that *FANCD2* overexpression was markedly associated with lymphatic invasion and the recurrence of high-grade EC. Cox regression and Kaplan-Meier analyses showed that high expression of *FANCD2* was associated with poor overall survival in patients with EC. In addition, a study also found that *FANCD2* expression positively associated with MSI in EC (44). This suggests that the overexpression of *FANCD2* may lead to the accumulation of MSI in endometrial cells, leading to genomic instability and eventually to the occurrence of EC. After *FANCD2* knockdown, the sensitivity of EC cells to paclitaxel, cisplatin and doxorubicin increased markedly, suggesting that *FANCD2* promotes EC cells (45), highlighting its prognostic value in EC. In summary, high expression of *FANCD2* may increase the risk of EC by affecting DNA damage repair and cell genome stability. In addition, overexpression of this gene is closely related to the poor prognosis of EC and *FANCD2* may be a valuable biomarker for evaluating the prognosis of patients with EC.

ii) FANCI. FANCI forms a heterodimer with FANCD2, which is then recruited to the site damaged by related proteins, thereby playing an important role in DNA damage repair (46). The absence of *FANCI* markedly downregulates the expression of core FA proteins such as FANCD2 and FANCB, leading to the accumulation of DNA damage within cells. Additionally, FANCI silencing partially reduced TP53 expression, causing cell cycle arrest at the G_1 phase (47). Research has shown that the mutation rate

of *FANCI* in EC is 8.70% (21). This is consistent with the observation by Zhao *et al* (48) that the mutation rate of the *FANCI* gene in EC exceeded 8%. Pan-cancer research using The Cancer Genome Atlas (TCGA) has found that somatic mutations in *FANCI* exist in multiple types of cancer. Of the 517 EC, 43 cases (8.32%) harbored mutations. In addition, Fierheller *et al* (49) reported a case of ovarian cancer carrying *FANCI* c.1813C > T in a patient with extensive genome-wide SCNA (50). Dong *et al* (51) identified FANCI mutations in the HR repair gene mutation spectrum of patients with uterine serous carcinoma. This suggests that type II EC are associated with HR repair defects caused by *FANCI* mutations. In addition, Bi *et al* (52) analyzed the TCGA dataset of patients with EC and found that *FANCI* overexpression may be associated with a poor prognosis in EC. *FANCI* may become a valuable biomarker for assessing the prognosis of patients with EC. Further research is needed to investigate the effect of *FANCI* on type I EC and the regulatory role of *TP53* in developing EC to clarify the function and underlying mechanisms of this gene in different EC subtypes and guide treatment strategies.

Downstream FA genes and EC

HR repair-related genes and EC

i) FANCN. FANCN, also known as PALB2, is closely associated with BRCA2 (53). The coiled-coil, WD40 and ChAM domains of PALB2 ensure the normal formation of RAD51 filaments and promote the correct binding of RAD51 to DNA, which is critical for the HR repair of DSBs (54). In addition, PALB2 interacts with BRCA1/2 to form the BRCA1-PALB2-BRCA2 axis, which promotes DSB repair, maintains genomic stability and is crucial for inhibiting tumor progression (55). Multiple studies have identified mutations that cause PALB2 loss of function in patients (56-61). Salomão *et al* (21) analyzed CBioportal data and found that the mutation rate of *FANCN* in EC was 6.62%. Johnatty *et al* (62) determined the role of *PALB2* mutations in increasing the risk of EC using a multigene panel detection. In 2019, one patient with EC with a pathogenic *PALB2* mutation was identified among 198 women in China (63). Sequencing analysis based on the TCGA-UCEC cohort revealed that the mutation frequency of the *PALB2* gene in EC cases was markedly higher than that in the general population, more than doubling (0.32 vs. 0.14%). Researchers also identified a patient with a pathogenic *PALB2* frameshift mutation (c.3116delA, p.Asn1039Ilefs) who was diagnosed with stage I endometrioid EC at 70 years of age (64). A *PALB2* gene mutation [NM_024675.3 (PALB2): c. (3113+1_3114-1)_(3201+1_3202-1) del] was identified in the tumor tissue of a patient with serous EC; this mutation is considered pathogenic (65). In addition, Foo *et al* (66) used whole-exome sequencing (WES) to discover that *PALB2* mutations in breast cancer patients can lead to multiple genomic SCNA. This suggests that the gene mutation may be associated with type II EC; however, further validation in patients with EC is required. Bowman-Colin *et al* (67) found that *PALB2* coordinates with the cell cycle factor Trp53 to inhibit breast cancer formation in mice, suggesting that *PALB2* mutations affect TP53 function and lead to cell cycle abnormalities. In summary, *PALB2* mutations are associated with both type I and type II EC; however, further investigation is needed into the specific pathways through which this gene regulates HR repair in endometrial cells and its impact on endometrial cell cycle regulation.

ii) FANCO. *FANCO*, also known as *RAD51C*, is a tumor suppressor gene. As a paralog of *RAD51*, this gene plays a central role in the HR repair of ICLs and DSBs by forming RAD51B-RAD51C-RAD51D-XRCC2 and RAD51C-XRCC3 complexes, which are critical for maintaining replication fork integrity (68-70). Additionally, this gene participates in the regulation of DNA damage-induced cell cycle S-phase checkpoint by activating the phosphorylation of CHK2 (68). Salomão *et al* (21) analyzed CBioportal data and found that the mutation rate of *FANCO* in EC was 3.21%. Ring *et al* (71) detected three cases of serous EC carrying *RAD51C* mutations among 381 EC patients using a multi-gene panel, suggesting that mutations in this gene may be associated with type II EC (serous carcinoma). Kondrashova *et al* (64) analyzed 30 known and candidate EC risk genes in patients with EC (TCGA-UCEC study) and the general population (gnomAD database) using tumor sequencing data and reported a nine-fold increase in the frequency of pathogenic or possible pathogenic variations in the HR repair-related gene *RAD51C* (0.97 vs. 0.1%). This study underscores the potential role of *RAD51C* in EC development and highlights its potential as a candidate gene for the future exploration of EC risks. In conclusion, clinical genomic data suggest that *RAD51C* mutation is associated with type II EC (especially serous carcinoma), but its role and related mechanisms in type I EC remain unclear. Additionally, the CHK2 phosphorylation regulatory pathway also needs to be further verified in endometrial cell models.

iii) FANCJ. *FANCJ*, also known as BACH1 and BRCA1 interacting protein 1 (BRIP1), is a key downstream gene of the FA pathway. This gene can bind to the carboxyl-terminus of BRCA1 to promote HR repair (72). Moreover, this gene can be recruited to DNA break sites and, together with CTLP, promotes DNA end resection and repair of ICL and DSBs (73,74). It also participates in cell-cycle regulation through phosphorylation and dephosphorylation states (75). Salomão *et al* (21) analyzed data from CBioportal and found that the mutation rate of *FANCJ* in EC was 7.37%. Heeke *et al* (60) used NGS600 sequencing to detect an *FANCJ* mutation rate of 0.14% in 1,475 patients with EC. At the same time, studies have shown that *BRIP1* has a higher mutation frequency in type II cancer than in type I cancer (76). Ring *et al* (71) reported the presence of a harmful germline mutation in *BRIP1* in 13 non-LS EC patients (p.Lys705Thrfs*10). de Jonge *et al* (77) reported *BRIP1* mutations c.632delC and P.Ro211fs in two EC patients with HR repair deficits. A frameshift mutation (p.Q554Hfs*35) in *FANCJ* was identified as pathogenic in high-grade EC (78). In addition, it has been found that *FANCJ* mutant mice show an increase in spontaneous MSI (79). This suggests that this may be related to type I EC. In summary, clinical genomic data suggest that *BRIP1* mutations are associated with EC and that the mutation frequency is higher in type II than in type I. However, the functional mechanism in type I EC remains unclear. Further research is needed to investigate the mechanism of *FANCJ*-mediated MSI in endometrial cells and the specific role of its phosphorylation in cell cycle regulation.

Table IV. Molecular function of FA gene and molecular abnormalities associated with EC.

Gene	Alias	Location	Mutation rate (%)	Molecular functions	Abnormalities associated with EC development
FANCE	*FACE*	6p21.22	4.54	Promotes DNA damage repair and genomic stability (21,29) and involved in cell cycle regulation (25)	Low expression (25) Overexpression (26) Mutations (24)
FANCC	*FAC*	9q22.3	5.10	Promotes DNA damage repair and genomic stability (24) and is involved in cell cycle regulation (24)	Mutations (21,29)
FANCA	*FAA*	16q24.3	8.88	Participates in DSB and ICL repair processes (35,36) and enhances the interaction between MSH2 and MLH1, participating in mismatch repair (37)	Mutations (21,38-41)
FANCD2	*FAD2*	3p25.3	9.07	Participates in the FA pathway by interacting with FANCI to form an ID2 complex (42)	Mutations (24) Overexpression (9,44,45)
FANCI	*KIAA1794*	15q26.1	8.70	Forms ID2 complex (46) and regulates FA core protein expression and the cell cycle (47)	Silencing (47) Mutations (49-51)
FANCN	*PALB2/ BRCA2*	16p12.2	6.62	Promotes the correct binding of RAD51 to DNA, participating in HR repair (54) and interacts with BRCA1/2 to form BRCA1-PALB2-BRCA2 axis, promoting DSB repair (55)	Mutations (62,64,66,67)
FANCO	*RAD51C*	17q22	3.21	Promotes HR repair by interacting with other RAD51 homologs and is involved in cell cycle regulation (68-70)	Mutations (64,71)
FANCJ	*BACH1/ BRIP1*	17q23.2	7.37	Binds to the carboxyl terminal of BRCA1 protein to promote HR repair (72) and promotes DNA end excision ICL and DSB (73,74)	Mutations (60,71,77,78)
FANCD1	*BRCA2*	13q13.1	15.31	Binds to PALB2, initiates DNA end resection and promotes RAD51 loading, collaborates with BARD1 to enhance RAD51 recombinase activity (80) and is involved in cell cycle regulation (80)	Mutations (77,84-86)
FANCS	*BRCA1*	17q21.31	9.26	Protects stalled DNA replication forks (81) and is involved in cell cycle regulation (80)	Mutations (77,84-86)
FANCR	*RAD51*	15q15.1	3.40	Promotes homology search and double-stranded exchange by binding to single-stranded DNA to form nuclear protein filament (87)	Mutations (21) Deletion (88) Polymorphism (89-93)
FANCU	*XRCC2*	7q36.1	3.02	Involved in HR repair of ICLs and DSBs (94,95)	Polymorphism (100,101) Mutations (98,99)
FANCW	*RFWD3*	16q23.1	4.73	Promotes the timely removal of RPA and RAD51 from DNA damage sites (102) and is involved in cell cycle regulation (80)	Mutations (21)

FA, Fanconi anemia; EC, endometrial cancer; DSB, DNA double-strand break; ICL, interstrand cross-linking; ID2, FANCI-FANCD2; HR, homologous recombination.

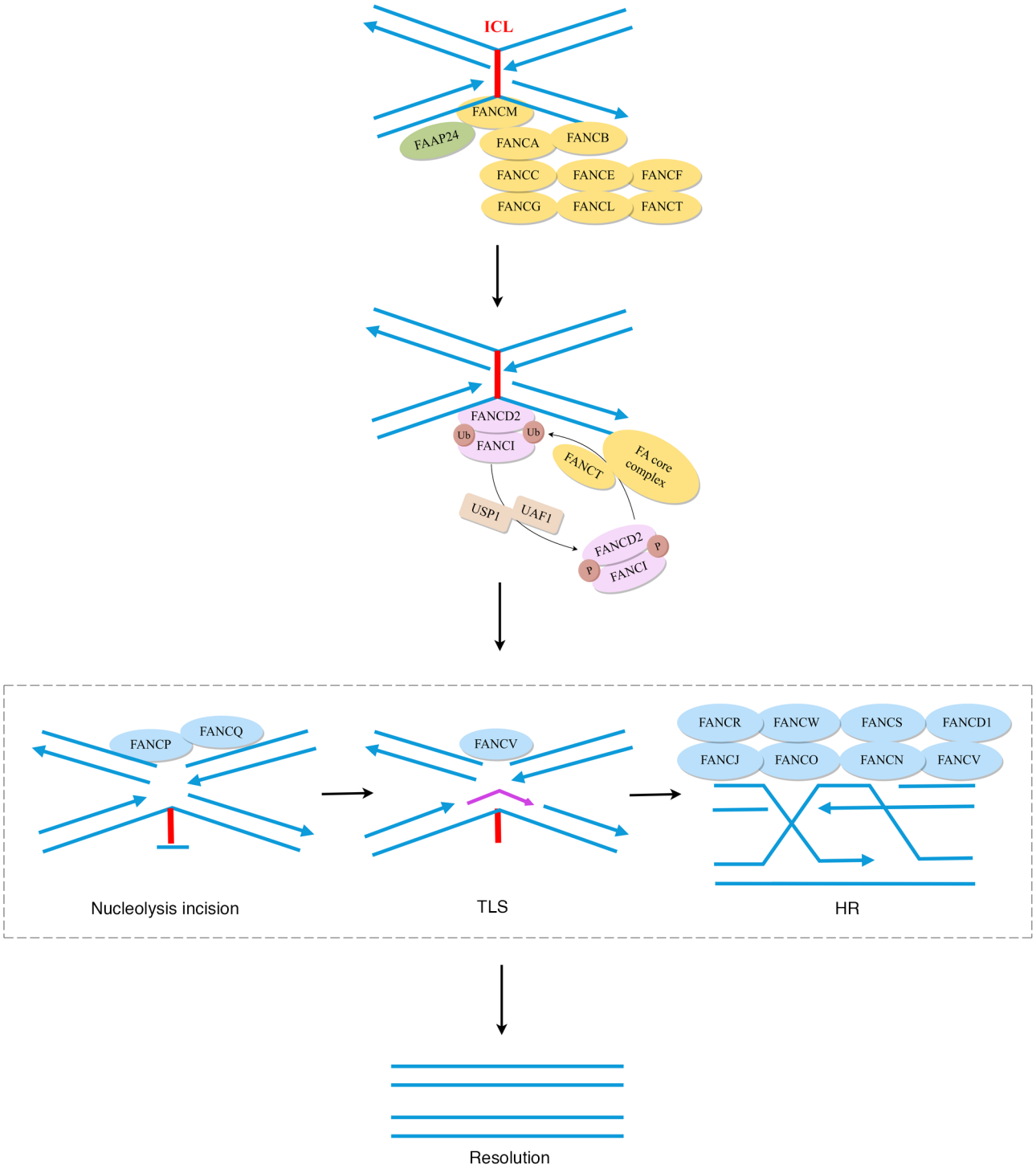

Figure 1. Mechanism of DNA damage repair by the FA pathway. By targeting FANCM, FAAP24 forms the FANCM-FAAP24 complex, which recognizes DNA ICL and promotes the recruitment of the FA core complex to the DNA damage site. Subsequently, the FA core complex and FANCT mediate monoubiquitination of the ID2 complex. Mono-ubiquitinated ID2 activates the downstream FA gene to coordinate nucleolytic incision, TLS and HR, the three key DNA repair processes that ultimately complete DNA damage repair. By Figdraw (www.figdraw.com). FA, Fanconi anemia; ICL, interstrand cross-linking; ID2, FANCI-FANCD2; TLS, trans lesion synthesis; HR, homologous recombination.

iv) FANCS and FANCD1. FANCS/BRCA1 and FANCD1/BRCA2 play key roles in DNA damage response through HR repair. BRCA1 is mainly localized at DNA damage sites, where it binds to PALB2 to initiate DNA end excision and promotes RAD51 loading. Additionally, BRCA1, in conjunction with BARD1, enhances the activity of the RAD51 recombinase, whereas BRCA2 protects against stagnant DNA replication bifurcations (80,81). In addition, BRCA1/2 interacts with TP53 to regulate cell cycle progression. Functional deficiency can lead to genomic instability, ultimately promoting cancer occurrence and development (82,83). Studies have shown that *FANCS/BRCA1* and *FANCD1/BRCA2* mutations are markedly associated with EC. Data analysis from CBioportal showed that the mutation

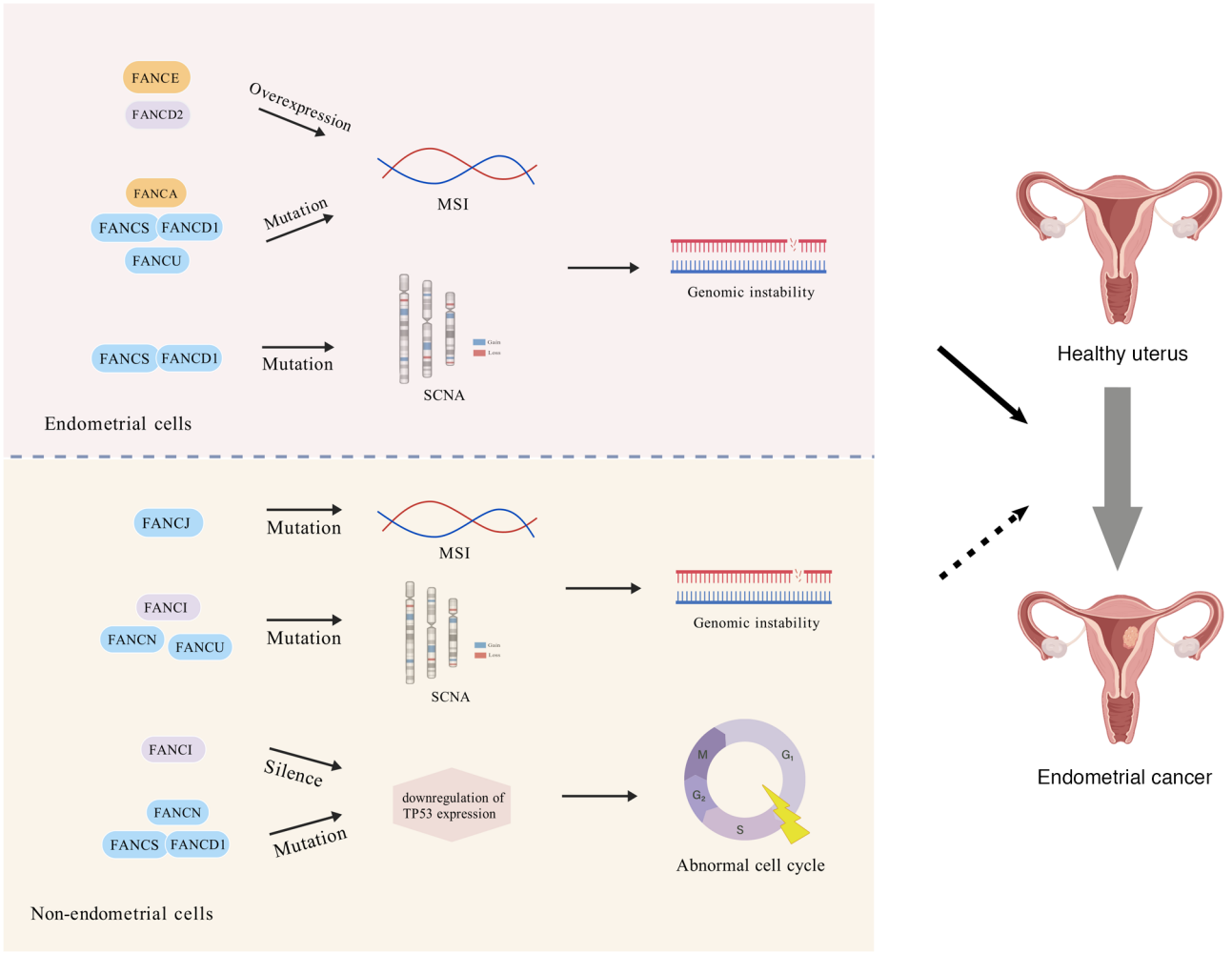

Figure 2. Related mechanisms of EC caused by FA gene abnormalities. In endometrial cells, overexpression of FANCE/D2 and mutations in FANCA/S/D1/U can lead to MSI, while mutations in FANCS/D1 can cause SCNA. These abnormalities all increase genomic instability, thereby driving the development of EC. In non-endometrial cells, FANCJ mutations can also cause MSI, while FANCI/N/U mutations can lead to SCNA. The two of these abnormalities also increase genomic instability. Additionally, FANCI silencing and FANCN/S/D1 mutations are associated with downregulation of TP53 expression, which can result in abnormal cell cycle progression and may ultimately contribute to the development of EC. By BioGDP (BioGDP.com). EC, endometrial cancer; FA, Fanconi anemia; MSI, microsatellite instability; SCNA. somatic copy number alterations.

rate of *FANCS* in EC was 9.26% and that of *FANCD1* was 15.31% (21). In a large cohort study of *BRCA1/2* mutation carriers, de Jonge *et al* (84) found that compared with the general population and non-*BRCA1/2* gene mutation carriers, *BRCA1/2* mutation carriers had a two- to three-fold increased risk of developing EC and *BRCA1* gene mutation carriers had the highest risk of developing rare serous and p53-abnormal EC subgroups. A recent study identified 35 patients with *BRCA1/2* copy number loss and eight patients with *BRCA1/2* somatic mutations among 187 high-grade ECs using shallow whole-genome sequencing (85). In addition, in a study by Smith *et al* (86), MSI or SCNA pathogenic *BRCA1/2* mutations were identified in 13 of 769 patients with high MSI or SCNA levels, whereas *TP53* mutations were identified in all patients. de Jonge *et al* (77) identified pathogenic variants of *BRCA1* and *BRCA2* in eight ECs with HR repair defects: *BRCA1*, c.4327C>T, p.Arg1443*; *BRCA2*, c.6373dupA, p. Thr2125fs c.6306_6413del; and *BRCA2*, p.Ser2103_Val2138del. In summary, the clinical data suggest that *BRCA1/2* mutations are associated with both Type I and Type II EC, with a more significant association with high-grade EC (Type II). However, the mechanisms underlying these mutations in high-risk subtypes, such as serous carcinoma, require further clarification. Additionally, the synergistic regulation of the cell cycle by *BRCA1/2* and *TP53*, as well as the mechanisms related to MSI and SCNA caused by *BRCA1/2* mutations, require further validation in endometrial cells.

v) FANCR. FANCR/RAD51 is an essential recombinase involved in HR repair that forms nuclear protein filaments by binding to single-stranded DNA, promoting the pairing of RAD51 with DNA sequences and participating in homologous search and chain exchange, which are essential for the maintenance of HR repair and genome stability (87). Bioportal data analysis shows that the mutation rate of *FANCR* in EC is 3.40% (21). Auguste *et al* (88) evaluated the degree of DNA damage in 116 patients with high-grade EC using immunohistochemistry. The results showed that complete deletion of *RAD51* resulted in severe DNA damage in 28 patients. In addition, several studies have suggested that *RAD51* 135G/C

and 135C/C polymorphisms may be related to the occurrence and development of EC (89-91). Michalska *et al* (92) suggested that the 135C/C polymorphism may be more closely associated with EC. Additionally, Krupa *et al* (93) found that the *RAD51* C/C genotype was closely associated with the incidence of EC in patients with higher levels of basal DNA damage. In summary, existing clinical data suggest that the absence of *FANCR*/*RAD51* is associated with high-grade EC (Type II), however, the role of this gene in Type I EC and the underlying mechanisms remain unclear. Furthermore, the specific molecular pathways through which *RAD51* 135G/C and 135C/C polymorphisms influence EC susceptibility require further validation.

vi) FANCU. FANCU, also known as XRCC2, plays a vital role in the HR repair of ICLs and DSBs (94,95). *XRCC2* is a potential tumor suppressor gene in mammals. Mutations in this gene can lead to defects in DNA damage repair and SCNA, thereby disrupting genomic stability (96,97). Bioportal data analysis showed that the *FANCE* mutation rate in EC was 3.02% (21). Nero *et al* (98) performed genome sequencing of 137 patients with recurrent EC and identified *XRCC2* mutations in 2.9% of the patients. Taylor *et al* (99) identified one *XRCC2* gene frameshift mutation case in 50 cases of MSI-H endometrioid adenocarcinoma. Additionally, *XRCC2* SNP-41657C/T (rs718282) and 4234G/C (rs3218384) increased EC susceptibility (100,101). In summary, the current study indicated that *FANCU*/*XRCC2* mutations and SNP polymorphisms increase the risk of EC. However, the specific pathogenic mechanisms by which *XRCC2* mutations drive the development of endometrioid adenocarcinoma and how SNP polymorphisms in this gene contribute to EC require further clarification. Additionally, the mechanism by which *XRCC2* deletion leads to SCNA requires further validation in endometrial cells.

vii) FANCW. FANCW, also known as RFWD3, is an E3 ubiquitin ligase that promotes the timely removal of RPA and RAD51 from DNA damage sites and plays a crucial role in DNA HR repair and maintenance of genome stability (102). *RFWD3* is also necessary to maintain a normal cell cycle and participate in the DDR by positively regulating p53. Knockdown of the *RFWD3* gene may lead to cell-cycle arrest (103,104). Mutations in the *FANCW* gene have been identified in various cancers, including EC, ovarian cancer and bladder cancer. Compared with other types of cancer (2.23% in ovarian cancer and 3.89% in bladder cancer), the mutation frequency of this gene in EC is relatively high (4.73%) (21). However, the mechanisms by which *RFWD3* regulates the participation of p53 in cell cycle regulation and causes genomic instability due to mutations in endometrial cells require further validation.

4. Summary and prospect

EC is the most prevalent cancer of the female reproductive tract and its incidence is increasing worldwide. Although the prognosis of patients with early- and low-grade EC is usually good, the outcomes of patients with advanced disease, deep muscle infiltration or metastasis and recurrence remain poor. The limited understanding of EC pathogenesis has hindered the development of effective diagnostic and therapeutic strategies. Based on the current WES of clinical EC patients with deletions or mutations in the FA gene, the present review identified a strong association between FA gene defects and EC, particularly high-grade EC (Table IV). The FA pathway is the core mechanism by which cells respond to inter-chain cross-linking (ICL) damage and maintain genomic stability and integrity (Fig. 1). In EC, defects in the FA gene lead to genomic instability and/or an abnormal cell cycle, thereby promoting tumorigenesis and progression (Fig. 2). Currently, research on the role of FA in EC primarily relies on clinical sample analysis and there is a lack of FA gene-deficient EC mouse models to validate the pathogenic mechanisms. In addition, the role of the FA gene in different EC subtypes and the associated mechanisms require further clarification. In this context, future studies should focus on establishing appropriate FA gene-deficient mouse models and refining EC subtypes to elucidate the complex pathogenesis of EC.

The present review described the pathogenesis of EC in terms of FA pathway abnormalities. An in-depth understanding of the molecular mechanisms of EC pathogenesis may facilitate the development of targeted therapies that specifically target key genes, leading to a more accurate treatment for EC, which may substantially improve the quality of life and survival of patients with high-grade and advanced EC. The present review provided new insights into the genetic factors and pathogenesis of EC and will facilitate the development of new EC treatments in the future.

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Availability of data and materials

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Authors' contributions

Conceptualization was performed by LZ and AH, and methodology by MY and CL. Literature search and analysis were performed by MY, CL, HP, KM, XL, QL, YQ and ZZ. Investigation was performed by all authors. MY and CL were responsible for software and AH was responsible for supervision. Visualization was performed by MY and CL and writing-review and editing by LZ and AH. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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