The Molecular Biology of Fanconi Anemia

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Abstract

Fanconi anemia is a rare autosomal recessive disorder characterized clinically by congenital abnormalities, progressive bone marrow failure, and a predisposition to malignancy. FA cells are sensitive to DNA cross-linking agents. Complementation analysis of FA cells using somatic cell fusion has facilitated the identification of eight complementation groups, suggesting that FA is a genetically heterogeneous disorder. Six genes (*FANCA, FANCC, FANCD2, FANCE, FANGF, FANCG*) have been cloned so far. The majority of affected patients belong to FA group A. Of the 32 unrelated Israeli patients with FA that we studied, 6 carried the *FANCC* mutations and 15 the *FANCA* mutations. Among the Jewish patients, ethnic-related mutations were common. Recent cumulative evidence suggests that the FA proteins are repair proteins. FANCC, FANCA and FANCG bind and interact in a protein complex found in the cytoplasm and nucleus of normal cells. FANCD2 exists in two isoforms; the long active form, FANCD2-L, is absent from FA cells of all complementation groups. FANCD2 co-localizes with *BRCA1* in nuclear foci, probably as part of a large genomic surveillance complex. Studies using FANCA and FANCC knockout mice suggest that bone marrow precursors express interferon-γ hypersensitivity and show progressive apoptosis. The definition of the molecular basis of FA in many affected families now enables prenatal diagnosis.

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Fanconi anemia is a rare autosomal recessive disorder characterized clinically by congenital abnormalities, progressive bone marrow failure, and a predisposition to malignancy [1]. FA cells are sensitive to DNA cross-linking agents such as mitomycin C and diepoxybutane. The disease has a worldwide prevalence of 1–5 per million and is found in all races and ethnic groups, with an estimated heterozygous mutation carrier frequency of 0.3–1% [2]. The identification of eight FA complementation groups and the recent cloning of 6 of the FA genes [3–8] have led us to considerable progress in FA research and better insight into the pathogenesis of the disease. The aim of the present review is to summarize the current understanding of the genetics and molecular biology of FA.

FA = Fanconi anemia

Clinical course of FA

The clinical course of FA has been extensively reviewed [1]. The common physical findings include abnormal skin pigmentation, growth retardation, radial ray or other skeletal malformations, microphthalmia, and renal or urinary tract malformations. The large range of organ systems affected implicates the FA genes in a general developmental process mandatory for normal human embryogenesis. About 40% of patients have no major physical anomalies.

The hematologic complications of FA include progressive bone marrow failure that usually develops in the first decade of life. Often thrombocytopenia or leukopenia appears before full pancytopenia. Erythropoiesis is usually fetal-like, with macrocytosis as well as high antigen and increased hemoglobin F levels.

Acute myeloblastic leukemia develops in at least 10–15% of patients with FA, and myelodysplastic syndrome in about 5% (average age 15 years). In addition, patients receiving androgen therapy for bone marrow failure are prone to liver tumors (average age 16 years). Later (average age 23 years), cancer of several organs, including the skin, gastrointestinal tract, and gynecologic system, may develop. The skin and gastrointestinal tumors are usually squamous cell carcinomas. Before the advent of bone marrow transplantation, many FA patients died of bone marrow failure even before they could develop cancer, so the actuarial risk of cancer may be even higher.

The clinical picture of FA is highly variable. Some patients present with a relatively mild phenotype, normal skeletal development, and subclinical hematopoietic abnormalities, surviving to the third or fourth decade. Others have a more severe phenotype, with skeletal abnormalities and early onset of bone marrow failure and cancer.

Diagnosis of FA

Cells from patients with FA exhibit increased spontaneous chromosomal aberrations and hypersensitivity to DNA cross-linking agents such as MMC and DEB. Similar spontaneous, chromosomal

MMC = mitomycin C
DEB = diepoxybutane

changes are observed in other inherited chromosome instability syndromes, such as Bloom's syndrome and ataxia telangiectasia, but they are not DEB-induced. The DEB test is highly sensitive and specific for FA, and serves as a diagnostic criterion. New diagnostic approaches have resulted from the cloning of FA genes. FA cells also have several other phenotypic abnormalities, such as defects in cell cycle regulation and apoptosis.

Cloning of the FA genes

Complementation analysis of FA cells using somatic cell fusion has facilitated the identification of eight complementation groups, suggesting that FA is a genetically heterogeneous disorder [9,10]. This genetic heterogeneity has been largely verified by molecular cloning of the FA genes, each complementation group representing a distinct gene. Six genes have already been cloned: *FANCA* [3], *FANCC* [4], *FANCD2* [5], *FANCE* [6], *FANGF* [7], and *FANCG* [8]. Of the first 100 FA patients classified by the European Fanconi Anemia Research Program, the majority (n = 71) belonged to the FA-A group [2] [Table 1]. Worldwide prevalence varies according to ethnic background: for example, most FA patients in the Afrikaans-speaking population of South Africa belong to group A, whereas in the Ashkenazi-Jewish population (Eastern European origin), group C is most frequent [2].

Fanconi anemia C gene

- **FANCC *gene and protein***

The *FANCC* gene was the first FA gene to be cloned by functional complementation of an Epstein-Barr virus-immortalized FA-C cell line [4]. As predicted by the complementation test, the *FANCC* cDNA corrects the MMC and DEB sensitivity of FA-C cell lines but does not correct the MMC sensitivity of FA cells derived from other FA groups. *FANCC* gene has been characterized [11] [Table 1]. The FANCC protein shows no homology to any protein of known function. It is primarily a soluble cytoplasmic protein, but a nuclear complex of FANCA and FANCC and other FA proteins has also been detected [2].

- **FANCC *mutations***

Mutation analysis of the *FANCC* gene in western countries has revealed a relatively small number of characteristic mutations [2]. In most patients, the mutations are clustered in three regions of the gene: exon 1, intron 4 and exon 14. The IVS4+4A>T mutation predominates in patients of Ashkenazi Jewish ancestry, accounting for more than 80% of cases of FA in this population [12]. The carrier frequency of this mutant allele in a selected Jewish population was determined to be 1.1% [13]. The 322delG mutation is found in patients of North European ancestry, particularly Holland. The relative prevalence of mutations in exon 14 and the high across-species conservation of this exon indicate that the carboxy terminal region of FANCC most likely contains a critical functional domain. Augmented mRNA expression has been observed in the skeletal system, suggesting a more specialized function of FANCC in bone development [14]

Table 1. The Fanconi anemia genes

Gene	Pathogenic mutations	Location	Exons	Protein (aa)	Prevalence* (%)
FANCA	>100	16q24.3	43	1455	71
FANCB	–	–	–	–	1
FANCC	10	9q22.3	14	558	7
FANCD1	–	–	–	–	1
FANCD2	5	3q25.3	44	1451	1
FANCE	3	6p21.3	10	536	4
FANCF	6	1p15	1	374	2
FANCG	18	9p13	14	622	13

* Based on the first 100 FA patients classified by the European FA Research Program.
aa = amino acids.

- ***Genotype-phenotype analysis for* FANCC**

In general, patients with mutations in intron 4 (IVS4-4A>T) or exon 14 (R548X, L554P) have a significantly earlier onset of hematologic abnormalities and poorer survival than patients with exon 1 mutations (322delG or Q13X,20). However, Japanese patients with the same IVS4-4A>T mutation have a milder phenotype [15]. The reason for this variability has not been elucidated. The molecular basis of the milder phenotype in patients with exon 1 mutations may be related to the observation that cell lines with the 322delG mutation express a truncated isoform of FANCC, resulting in partial correction of MMC sensitivity, whereas cell lines with intron 4 mutations lack this isoform [16].

Fanconi anemia A gene

- **FANCA *gene and protein***

The *FANCA* gene was cloned by two techniques independently: functional complementation of an EBV-immortalized FA-A cell line [17] and positional strategy [2] [Table 1].

The FANCA protein contains a nuclear localization signal at its N-terminus and a partial leucine zipper motif between amino acids 1069 and 1090. The importance of the leucine zipper region remains unclear. Mutational screens have shown that the region of the FANCA protein from amino acids 1046 to 1320, encoded by exons 32-39, appears to be critical to FANCA function. Multiple patient-derived missense mutations have been identified in this region [18–20].

- **FANCA *mutations***

More than 100 private and semi-private mutations have been identified so far in the *FANCA* gene [18–23]. A high proportion (roughly one-third) are deletions, owing to the frequent occurrence of *alu* repeats at the deletion breakpoints [24,25]. Somatic mosaicism due to reversion of the pathogenic allele to wild-type has been described in *FANCA* and *FANCC* [26].

- ***Genotype-phenotype analysis***

Analysis of the FANCA mutations by the European Fanconi Anemia Research Group suggested that complete loss of the FANCA protein

EBV = Epstein-Barr virus

is associated with a severe phenotype, whereas alteration of the protein is associated with a milder phenotype, with later age at onset of aplastic anemia [27].

Fanconi anemia G gene

The *FANCG* gene was recently cloned and found to be identical to the previously cloned human *XRCC9* gene [8] [Table 1]. The FANCG protein is an orphan protein that contains an internal leucine zipper as its only recognizable motif. More than 20 mutations have been identified so far. All types of mutations have been found, with the exception of large deletions. One missense mutation in a possible leucine zipper motif may affect FANCG binding of *FANCA* [28]. A relatively early occurrence of acute lymphoblastic leukemia has been seen in patients in group G compared with patients in groups A and C [2].

Fanconi anemia group E gene

The *FANCE* gene was recently cloned [6] [Table 1].

Fanconi anemia group F gene

The gene mutated in Fanconi anemia group F was identified by complementation cloning. *FANCF* has no introns and encodes a 374 amino acid polypeptide with homology to prokaryotic RNA binding protein ROM [7] [Table 1].

Fanconi anemia D2 gene

Complementation group D is heterogeneous, consisting of two distinct genes, *FANCD1* and *FANCD2*. Recently, *FANCD2* was positionally cloned [5] [Table 1], and found to have two isoforms. It has no known functional domains but, unlike other known FA genes, is highly conserved in *Caenorhabditis elegans* and *Drosophilia*.

The mutational spectrum in Israeli FA patients

We studied 32 unrelated Israeli patients with FA (22 Jewish and 10 Arab) [Table 2], who were either treated at the Hematology Clinic of Schneider Children's Medical Center or referred to us from different pediatric hematology units throughout the country. Six bore *FANCC* mutations and 15 had *FANCA* mutations. Among the Jewish patients, ethnic-related mutations were common: IVS4+4 in the Ashkenazi Jews, 2172-2173insG and 4375delT in the Moroccan Jews [30], 890-893del was found in the Jewish-Tunisian patients and 2474C>G in the Jewish-Indian patients. In seven of the nine Arab patients the FA mutations were not identified, however neither the *FANCC* nor the *FANCA* genes are apparently involved.

Table 2. FA Mutations in Israeli patients

Complementation Group	Mutation	No. of alleles involved	Origin
FANCC	IVS4+4A>T	12	Ashkenazi-Jewish
FANCA	2574C>G	4	Indian-Jewish
	2172-2173+G	14	Moroccan-Jewish
	890-893del	3	Tunisian-Jewish
	4257delT	3	Moroccan-Jewish
	IVS42- 2GC,	2	Arab
	Val229Ile	2	Arab
	Del ex6-31	2	Arab
	Total	**42**	

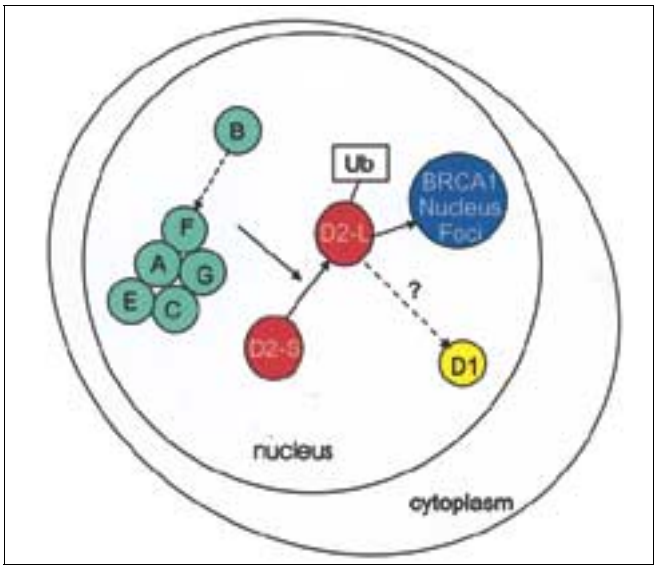

Figure 1. FA pathway of genomic stability. The products of 5 FA genes – *FANCA, FANCC, FANCE, FANCF, FANCG* – assemble into a nuclear complex. Complex formation is essential to the attachment of a single ubiquitin moiety to form D2-L (long form). Active D2-L binds to BRCA1 at the nuclear foci.

Cloning of the FA genes and pathogenesis of the disease

The availability of FANCC knockout mice has provided some clues to the pathogenesis of bone marrow failure. The study of FA genes recently led to the development of a model of molecular interactions.

Animal models of FA

Mice models with targeted disruptions of the *FANCC* and *FANCA* genes have been developed. However, the resulting mutants exhibit only part of the FA human phenotype. Cells derived from these animals show the classic hypersensitivity to bifunctional DNA cross-linking agents. Mice also display hypogonadism and reduced fertility [29]. Hematopoiesis, which is typically compromised in FA patients, appears to be unaffected in mice, but the repopulation capacity of the FANCC mutant stem cells upon serial transplantation is reduced. In addition, although no peripheral blood abnormalities were detected, an age-dependent decrease in burst-forming unit-erythroid and colony-forming unit granulocyte macrophage progenitors was found. In addition, the hematopoietic progenitor cells revealed a distinct hypersensitivity to interferon gamma [30]. Increased cell susceptibility to IFN-γ leads to *fas*-induced apoptosis, and the cells derived from the FANCC knockout mice exhibited a high level of *fas* expression at a low INF-γ concentration [31]. It has recently been shown that functional correction of FA-C cells with FANCC suppresses the expression of INF-γ-inducible genes [32]. This suggests that INF-γ hypersensitiv-

IFN-γ = interferon gamma

ity may be the major pathogenic mechanism underlying the development of progressive aplastic anemia in patients with FA. The relationship between this phenotype and the cellular response to DNA cross-linking is still obscure.

Molecular interactions of FA proteins

Cumulative evidence over recent years shows that FA proteins participate in a novel cellular pathway. FANCC, FANCA and FANCG bind and interact in a protein complex found in the cytoplasm and in the nucleus of normal cells [33,34].

The prospects for understanding the FA pathway have greatly improved with the identification of FANCD2 [4]. Higura et al. [35] suggested that the FANCD2 protein exists in two isoforms: the primary translation product (short FANCD2-S) and a higher molecular weight form (long FANCD2-L). The long isoform has a single ubiquitin moiety attached to a highly conserved residue at position 561. FANCD2-L is absent from FA cells of all complementation groups (except D1), but it reappears after correction of the FA genetic defect.

In wild-type cells, FANCD2 and BRCA1, a DNA damage-response agent and the major breast cancer susceptibility protein, have been found together in the same nuclear foci. Although the manner in which FA proteins intermingle with the BRCA1-associated proteins is not clear, the FA protein is apparently a repair protein. It seems that BRCA1 facilitates FA downstream reactions, possibly in combination with other DNA repair proteins that are associated with BRCA1 in a large genome surveillance complex [35].

FA like xeroderma pigmentosum and hereditary non-polyposis colorectal cancer is, therefore, a caretaker-gene disease [2] featuring genomic instability in combination with a strong predisposition to cancer [Table 3].

Cloning of FA genes: implications for diagnosis

Although the DEB test is highly sensitive and specific for the diagnosis of FA, it fails to identify heterozygote carriers of mutant FA genes. Detection of the majority of the FA genes has allowed for prenatal diagnosis. The identification of common mutant alleles in each ethnic group contributes to rapid diagnosis.

Genotype/phenotype correlations are also important for FA management. If a severe phenotype is diagnosed, patients may be treated more aggressively with bone marrow transplantation or gene therapy.

Table 3. Caretaker-gene diseases

Disease	No. of suspected genes	Molecular process
Ataxia telangiectasia	1	DNA damage response
Bloom syndrome	1	DNA unwinding
Werner syndrome	1	DNA unwinding
Xeroderma pigmentosum	7	Nucleotide excision/ transcription-coupled repair
Hereditary non-polyposis colorectal cancer	5	Mismatch repair
Hereditary breast/ovarian cancer	3	DNA-damage response repair, recombination, transcription
Fanconi anemia	7	?

Cloning of FA genes: implication for therapy

Allogeneic BMT from a human leukocyte antigen-matched sibling donor offers the only possibility of cure for the hematologic manifestations of FA (aplasia or bone marrow dysplasia). Low doses of cyclophosphamide and radiation must be used to avoid severe toxicity due to the chemo- and radiosensitivity in patients with FA [36]. Data from multiple institutions (over 150 patients) suggest an overall 2 year survival rate of 66% [37,38]. Despite success in treating FA aplasia by stem-cell replacement, some survivors show late development of secondary malignancies, particularly of the head and neck [37].

Most patients do not have an HLA-identical donor and are dependent upon the identification of suitably matched non-sibling relatives or unrelated donors. A study of 69 FA patients who underwent BMT from alternative donors showed a 3 year survival rate of 33%, graft failure being the most serious complication. Preliminary results based on the addition of fludarabine to the preparative regimen are encouraging [39].

An alternative in the absence of a histocompatible donor is the retroviral transfer of a FA gene into the hematopoietic stem cell. In current gene therapy trials, retroviral vectors expressing wild-type *FANCC* or *FANCA* are used to transduce the peripheral blood leukocytes of FA patients [2]. Once in the patient's bloodstream, the gene-corrected stem cells presumably initiate and support proficient hemopoiesis. A major obstacle to successful gene therapy is the poor efficiency with which the rare hematopoietic stem cells are transduced. To increase the number of these cells, many centers have initiated programs for the collection and cryopreservation of hematopoietic stem cells from FA patients before the onset of aplasia. Subsequent difficulties may include unstable expression of the transgene due to gene silencing and immunologic attack of the transduced cell, which expresses a protein that the body might identify as foreign.

Although useful, gene transfer studies, like BMT, cannot ameliorate the developmental abnormalities or cancer risk in non-hematopoietic tissues in patients with FA.

Conclusions and future trends

Cloning of the FA genes has opened a window to our understanding of the molecular basis of Fanconi anemia. It is now known that the FA complexes function upstream of FANCD2, which, in modified form, acts together with the *BRCA1* gene in the DNA-damage response pathway. The FA core complex might act as a sensor of DNA damage, leading to activation of FANCD2, which could be a crucial effector molecule in the circuit. Nevertheless, many questions remain unanswered: How does the FA core complex respond to DNA damage? How does modification of the FANCD2 target this molecule to *BRCA1*-containing foci? What precisely does FANCD2 do upon translocation to these sites?

BMT = bone marrow transplant
HLA = human leukocyte antigen

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