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Fanconi Anemia: A Signal Transduction and DNA Repair Pathway

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Fanconi anemia (FA†) is a fascinating, rare genetic disorder marked by congenital defects, bone marrow failure, and cancer susceptibility. Research in recent years has led to the elucidation of FA as a DNA repair disorder and involved multiple pathways as well as having wide applicability to common cancers, including breast, ovarian, and head and neck. This review will describe the clinical aspects of FA as well as the current state of its molecular pathophysiology. In particular, work from the Kupfer laboratory will be described that demonstrates how the FA pathway interacts with multiple DNA repair pathways, including the mismatch repair system and signal transduction pathway of the DNA damage response.

INTRODUCTION AND CLINICAL ASPECTS OF FA

Fanconi anemia (FA) is an autosomal and X-linked recessive disorder characterized by bone marrow failure, acute myelogenous leukemia (AML), solid tumors, and developmental abnormalities. At the molecular level, cells derived from FA patients display hypersensitivity to DNA cross-linking agents, resulting in increased numbers of chromosomal abnormalities, including translocations and radial chromosomes. This hypersensitivity made treating FA patients a challenge in the past because traditional treatments of their

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†Abbreviations: FA, Fanconi anemia; AML, acute myelogenous leukemia; SCT, stem cell transplant; FAB, French-American-British; FANC, Fanconi anemia complementation group; MMC, mitomycin C; GVHD, graft versus host disease; HPV, human papilloma virus, ATM, ataxia telangiectasia mutated; ATR, ataxia telangiectasia related.

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symptoms resulted in more harm than good. Recent years have revolutionized the care of the FA patient with modern blood banking, antibiotics, and hematopoietic stem cell transplantation (SCT), which has been performed on FA patients for almost 30 years [1]. Even with the greater survival of children into adulthood as a result of SCT, the specter of potential of solid tumors, such as squamous cell carcinomas of the head, neck, and genitourinary track, remains a serious problem [2,3]. Even though the classic features of thumb abnormalities and radius absence generally characterize these patients, FA children typically present in the first decade of life upon recognition of aplastic anemia [4,5]. Even more interesting is the fact that a sizable subset of FA patients has no discernible abnormalities at all, in a fraction estimated at up to one-third. As a result, the index of suspicion of the clinician must be high to recognize the potential for the diagnosis of FA in the wake of aplastic anemia.

The gold standard tests for FA quantify chromosomal breakage in cells exposed to cross-linking agents to which FA cells are hypersensitive, typically diepoxybutane [1,5]. On occasion, despite the strong suspicion of FA being present in a patient, the chromosome fragility test can be negative due to somatic reversion [6,7]. In the face of this possibility, if a negative diepoxybutane or MMC result has been obtained in the setting of strong suspicion of an FA diagnosis, then a skin biopsy should be obtained for culture and subsequent diepoxybutane testing.

Ninety percent of FA patients first present with bone marrow failure, but a percentage nonetheless display AML as the first evidence of FA. These cases of AML are typically M1-M4 FAB subtype and display no characteristic cytogenetic or molecular abnormality, although numerous translocations, deletions, and other aneuploidogenic changes can be found [8]. Some report a distinctly different spectrum of clones in FA versus sporadic AML [9]. Patients cannot be treated in a typical fashion as other AML patients because of intolerance of standard doses of alkylating agents. Thus, morbidity to the patient precludes an aggressive approach [10].

FA patients are at markedly increased risk of squamous cell carcinomas of the head and neck and genitourinary tract. These tumors have been only sporadically positive for human papilloma virus (HPV), although vaccination for HPV is strongly encouraged in the FA population. In addition, routine laryngoscopy and ENT follow-up is considered standard care for FA patients [2,3]. Breast cancer is also a cancer typical of adult FA patients, which is in line with the fact that 5 FA genes are actually familial breast cancer genes: *BRCA2, PALB2, RAD51C, SLX4*, and *BACH1* [11,12,13,14].

Because the FA patient is at increased risk of toxicity from SCT regimens, clinicians must assess the best scenario in which to undertake the procedure based on pre-empting the onset of leukemia, avoiding the long-term effects of blood product provision, and proceeding when the patient is in good clinical shape and unaffected by serious infections, such as those from invasive organisms like *Aspergillus*. An attempt to identify the complementation group and gene mutation should be made in order to assess the suitability of a family member stem cell donor in order to avert the possibility of that donor having a subclinical case of FA. It has become clear from the experience of FA clinicians that FA-D1 and those with the Ashkenazi FANCC mutation patients are at significant and early risk of progression to AML, often before the presentation of aplastic anemia [15]. In general terms, it is thought that such a risk of early AML progression is coincident with a more severely displayed FA phenotype [16,17,18].

Historically, the challenges of SCT in FA patients have been numerous. The issue of graft failure has been a significant issue with a prevalence of 10 percent, but use of fludaribine has shrunk this number in recent years to less than 1 percent. As a result, efforts at reduction of conditioning have been steady, and the use of total body irradiation has been diminished down to doses of 400 to 600 cGy. In addition, the use of cyclophosphamide has also been decreased in recent years. With an allogenic-related transplant, the long-term survival is often greater than 80 percent [18,19]. Secondary effects of SCT predictably have greater

Table 1. Summary of the Fanconi Anemia pathway, genes, proteins, and functions.

Complementation Group	Gene	Chromosome location	Protein weight (kD)	Motifs	Required for D2 monoubiquitination
A	*FANCA*	16q24.3	163	NLS, NES	yes
B	*FANCB*	Xp22.31	95	NLS	yes
C	*FANCC*	9q22.3	63	none	yes
D1	*FANCD1/ BRCA2*	13q12.13	380	BRC repeats	no
	FANCD2	3p25.3	155/162	none	yes
E	*FANCE*	6p21.22	60	NLS	yes
F	*FANCF*	11p15	42	none	yes
G	*FANCG/ XRCC9*	9p13	68	TPRs	yes
I	*FANCI/ KIAA1794*	15q25-26	146	none	yes
J	*FANCJ/ BRIP1/ BACH1*	17q22-24		ATPase/ helicase	no
L	*FANCL/ PHF9*	2p16.1	43	E3 ligase	yes
M	*FANCM*	14q21.3	250	ATPase, DNA translocase	
N	*FANCN/ PALB2*	16p12	130	WD40	no
O	*FANCO/ RAD51C*	17q23	37	RAD51 paralog	no
P	*FANCP/ SLX4*	16p13.3	268	endonuclease	no
Q	*FANCQ/ XPF4/ ERCC4*	16p13.12	100	endonuclease	no

consequences for FA patients, presumably because of their underlying issues of growth delay, endocrine dysfunction, and risk of malignancy, all of which are associated with long-term effects of undergoing SCT. A markedly increased risk of acquisition of squamous cell carcinoma is seen post-transplantation, out of proportion to that observed in FA patients, and are only somewhat linked to human papillomavirus and linked to GVHD [3].

The idea that FA cells are hypersensitive to endogenous and exogenous stimuli suggests that FA stem cells in the bone marrow are susceptible to a sort of "natural selection." This is probably why somatic reversion is observed in some FA patients. As a result, it has been postulated that FA patients are ideal for gene therapy clinical trials. Trials entailing the most common complementation group, FA-A, have been instituted using a lentiviral transduction system of hematopoietic stem cells from FA patients, manipulated *ex vivo*. *In vitro* data suggest that hematopoietic stem cells can be transduced with subsequent colony-forming assays suggesting increased growth and reconstitution. Such trials have been disappointing, however, because lack of permanent transduction of progenitors has led to failure to establish long- term hematopoiesis [20,21].

Traditionally, androgens have proved to be an efficacious treatment in aplastic patients, FA patients included. Androgens generally stimulate more effective hematopoiesis, resulting in an increase in peripheral blood counts. The use of androgens has been marked by their difficulty in use in females, however, given the masculinizing side effects. In addition, their use has been associated with increased risk of liver adenomas [22,23].

MOLECULAR PATHOPHYSIOLOGY OF THE FA PATHWAY

The FA pathway is composed of at least 16 genes [24]. Each of these genes, when biallelically mutated, causes FA, except for the X linked FANCB. The encoded proteins (Table 1) can be subdivided within the FA pathway into three groups: 1) proteins (FANCA, B, C, E, F, G, L, M) that make up the core complex; 2) the FANCD2 and FANCI proteins, which compose the ID complex that is monoubiquitinated after DNA damage; and 3) five downstream effector proteins, FANCD1/BRCA2, FANCJ/BRIP1/BACH1, FANCN/PALB2, FANCO/SLX4, and FANCP/RAD51C that likely participate directly in DNA repair [24,25,26]. The downstream FA proteins include classic, familial breast cancer genes, thus providing overlap of FA biology with homologous recombinatorial pathways that include BRCA1/2, PALB2, SLX4, and RAD51C. These proteins appear to have an assortment of functions that include helicase and endonuclease activity, resulting in the loading of RAD51 onto double strand breaks. Additional work has demonstrated the ability to activate the translesion synthesis pathway, allowing the bypass of polymerases past structurally obstructive repair intermediates [25,27,28]. The FA pathway also interacts with the DNA damage response through the DNA sensing and signaling proteins ataxia telangiectasia mutated (ATM) and ATM-related (ATR) kinases and Chk1 kinase. Patients with biallelic mutations of the ATR kinase develop Seckel's syndrome, an extremely rare autosomal-recessive disease characterized by chromosome breakage, microcephaly, growth retardation, mental retardation, and leukemia, suggesting it is at least an FA variant. Interestingly, major sites of ATR-mediated phosphorylation are found on FANCA, FANCD2, FANCG, and FANCI [29,30,31,32].

Teleologically, the involvement of very specific developmental abnormalities in FA patients implies that the FA proteins have the potential for other functions aside from those they perform in protecting the genome. Some have argued that the main function of the FA pathway is to regulate oxidative stress, because reactive oxygen species have been documented to be involved in bone marrow failure [33,34], cancer [35], endocrinopathies [36], abnormalities in skin pigmentation [37], and malformations [38]. This explanation becomes even more plausible when considering the redox-related functions of some FA proteins [39,40]. Recent provocative work has supported the idea that acid aldehydes are the toxic metabolite *in vivo*, as mouse models knocking out enzymes that detoxify such chemicals phenocopoy FA [41].

STUDIES FROM THE KUPFER LABORATORY

The Kupfer laboratory has focused on three main areas of FA biology. The first area has been the characterization of FA protein localization to chromatin. We noted in 2001 that immunofluorescence microscopy

revealed that FANCA was nuclear but nonnucleolar and there was not localization to chromosomal material at condensation. Immunoblotting of chromatin extracts confirmed this localization to chromatin. Our data at that time were the first demonstration of FA protein localization to chromatin and an emphasis that the FA pathway consisted of DNA repair proteins, although the enzymology thereof was still unknown.

During this time, we noted that the FA core complex behaved in the same way in the chromatin localization. In fact, we then noted that this localization was in a DNA dependent fashion. In simple but elegant experiments, a postdoctoral fellow in the lab, Jun Mi, executed chromatin fiber experiments that showed beads and coating of FA proteins aggregating along the fibers, and markedly increased protein could be visualized after crosslinker treatment [42].

Concomitant with this work was the demonstration that the FA pathway was in and of itself a signal transduction pathway. During my postdoctoral work, I identified the binding of the FA core complex with CDC2, the mitotic cyclin dependent kinase [43]. As an extension, we utilized mass spectroscopy to identify phosphorylation sites on FA proteins. Over the course of the last several years, we have reported on the characterization of at least five different phosphorylation events. Two sites on FANCG appear to be responsible for the detachment of the core complex from condensed chromatin [44]. Three others on FANCG, FANCA, and FANCD2, respectively, are DNA damage inducible, suggesting that they fit into the response to damage through ATR, CHK1, and other kinases [45,46,47]. A great advantage of working with FA as a genetic model is that the mutant cells can be complemented using cDNAs. As a result, these cDNAs can be modified at phosphorylation sites via PCR directed mutagenesis, and they can be tested for complementation. In this fashion, we have been able to confirm that the mapped phosphorylation sites are functionally important, since abrogation results in near or complete loss of resistance to crosslinkers. Further, in the case of the core complex, biochemical evidence of complementation can be shown as well with respect to FANCD2 monoubiquitination. Intriguingly, replacement of the phosphorylated amino acid with a phosphomimetic amino acid such as aspartic acid results in retention of the resistance phenotype, as we observed in our characterization of the phosphorylation at FANCA serine 1449.

Our third endeavor has focused on the binding of FA proteins with other proteins of defined function or involved in specific pathways. Using mass spectroscopy, we have identified two binding proteins critical for DNA damage response. We have shown that FANCD2 and RAD18 bind in a FANCD2 monoubiquitination-dependent manner [48]. RAD18 is known to ubiquitinate PCNA in a DNA damage-inducible fashion as well, and such a response invokes activation of the translesion synthesis pathway, allowing for bypass of the replication fork around obstructive lesions, with homologous recombination coming in downstream of this process. HR function is also coordinated by FANCD2 via its interaction with BRCA2 and PALB2. Knockdown of RAD18 results in an FA phenotype for survival, chromosomal breakage, and FANCD2 monoubiquitination.

A second pathway we have identified involves the mismatch repair system [49]. Both MSH2 and MLH1 are FANCD2-binding proteins, and loss of both results in an FA-like phenotype. Functionally, cells mutant for the FA pathway also resemble MMR mutants in their deficiency in a functional mismatch repair plasmid assay.

I have been at Yale for the past 6 years, so thus am a relative newcomer to the rich fabric of DNA repair as it has existed here. However, my laboratory has already established numerous fruitful collaborations with other DNA repair-focused teams. For example, our work on RAD18 has enlisted expertise from Patrick Sung's group, and Peter Glazer has been an active participant in our mismatch repair work. We also have active collaborations under way with Rogers, Sweasy, and others. The atmosphere here is vibrant and amazingly conducive to our research mission. Future work includes focus

on the cell biology complement to biochemistry of the FANCD2-FANCI ubiquitination reaction as well as the FANCM-FAAP24 engagement of chromatin.

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