PERSPECTIVE

The Fanconi road to cancer

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Study of rare human genetic diseases often leads to significant advances in the understanding of cancer biology in general. Such is the case for Fanconi Anemia (FA), a rare cancer susceptibility syndrome with an incidence of only 1 in 300,000 live births. FA is an autosomal recessive disease characterized by chromosome instability, cellular hypersensitivity to DNA cross-linking agents such as Mitomycin C (MMC) and Cisplatin, and increased predisposition to cancers, mainly leukemias and squamous cell carcinomas of the head and neck or gynecologic system (Alter et al. 2003; Bagby 2003). Although the function of the seven cloned FA genes (A, C, D1, D2, E, F, and G) is largely unknown, the genes cooperate in a common cellular pathway, known as the FA/BRCA pathway (D'Andrea and Grompe 2003). The recent identification of the breast and ovarian cancer susceptibility gene, *BRCA2*, as the *FANCD1* gene (Howlett et al. 2002) implicates the FA/BRCA pathway in homology-directed DNA repair (HDR), and suggests that disruption of the pathway may promote breast and ovarian cancer. In the current issue of *Genes and Development*, Houghtaling et al. (2003) analyze mice with a targeted deletion of one of the downstream FA genes—namely, *Fancd2*. Their analysis defines a role for the FA pathway in HDR and (at last) provides a molecular link between the FA pathway and epithelial cancers.

Several recent studies have defined molecular interactions among the FA proteins in the pathway (Fig. 1; for review, see D'Andrea and Grompe 2003). Five of the FA proteins (A, C, E, F, and G) form a nuclear complex (Garcia-Higuera et al. 1999; Medhurst et al. 2001) required for the activation (monoubiquitination) of the downstream FANCD2 protein (Garcia-Higuera et al. 2001). This FA protein complex either has intrinsic monoubiquitin ligase activity or it regulates a monoubiquitin ligase. Following DNA damage by cross-linking agents, FANCD2 is monoubiquitinated and targeted to chromatin-associated foci, where it interacts with the breast cancer protein, BRCA1 (Garcia-Higuera et al. 2001) and the MRE11/RAD50/NBS1 (M/R/N) complex (Nakanishi et al. 2002). Moreover, the BRCA1/BARD1 heterodimeric ubiquitin ligase complex (Brzovic et al. 2001) is required for the efficient assembly of these foci (A. D'Andrea, unpubl.). Disruption of the FA/BRCA pathway results in

chromosome instability, DNA cross-linker hypersensitivity, and the common clinical features of FA.

FA-D1 patients have biallelic mutations in *FANCD1/BRCA2* (Howlett et al. 2002; Stewart and Elledge 2002). *BRCA2* functions further downstream in the FA/BRCA pathway, and, unlike other FA proteins, appears to play a more direct role in DNA repair. *BRCA2* binds to single- and double-strand DNA (Yang et al. 2002) and binds to RAD51 through its BRC regions (Marmorstein et al. 1998). Moreover *BRCA2* regulates the activity of RAD51, by controlling nucleoprotein filament formation (Davies et al. 2001). Loading of RAD51 on single-strand DNA by *BRCA2* is required for the early events in homologous recombination repair, such as strand invasion. Biallelic inactivation of *BRCA2* results in a cellular defect in HDR (Moynahan et al. 2001). Perhaps not surprisingly, biallelic null mutations in *BRCA2* in humans or *Brca2* in mice result in embryonic lethality. Cells derived from FA-D1 patients, however, have hypomorphic alleles of *FANCD1/BRCA2*, expressing truncated *BRCA2* polypeptides with partial activity (Howlett et al. 2002). These FA-D1 individuals survive gestation but die in early childhood.

Murine knockout models for FA genes

To date, murine knockout models of several *Fanc* genes, including *Fancc* (Chen et al. 1996; Whitney et al. 1996), *Fanca* (Rio et al. 2002), and *Fancg* (Yang et al. 2001) have been generated. Although these FA mice exhibit some phenotype features of human FA patients (i.e., chromosome instability, defective germ cell development), they do not spontaneously develop anemia or cancer. The phenotypes of these knockout mice are essentially indistinguishable (Noll et al. 2002), consistent with a model (Fig. 1) in which the FA protein complex components cooperate to perform a common function. Because of the more downstream role of *Fancd2* in the FA pathway, Houghtaling et al. (2003) postulated a more critical role of *Fancd2* in murine development and carcinogenesis. As predicted, the *Fancd2*^{-/-} mice do indeed exhibit a more severe phenotype.

Specifically, the *Fancd2*^{-/-} mice exhibit microphthalmia (small eyes), perinatal lethality, and more severe hypogonadism than the *Fanca*-, *Fancg*-, or *Fancc*-deficient mice. Strikingly, the *Fancd2*-deficient mice have an increased incidence of epithelial cancers (i.e., breast, ovarian, and liver cancers), similar to the tumor spectrum

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Figure 1. Cooperative interaction of the FA proteins and BRCA proteins in a common pathway. The FA proteins (A, C, E, F, G) are assembled in a nuclear protein complex. Recent studies have indicated that the Bloom's helicase, BLM, is also a subunit of the complex. The FA complex is required for the monoubiquitination of the downstream FANCD2 protein. The FA monoubiquitination ligase activity of the FA complex is activated by DNA damage, perhaps through the activity of an upstream "sensor" kinase. Monoubiquitinated FANCD2 is targeted to chromatin-associated nuclear foci where it assembles with the breast cancer susceptibility proteins, BRCA1 and BRCA2. These nuclear foci also contain the RAD51 protein and the MRE11/RAD50/NBS1 (M/R/N) complex. The ubiquitin ligase (BRCA1/BARD1) heterodimer is required for the efficient assembly of these chromatin foci; accordingly, *BRCA1*^{-/-} tumor cells have decreased FANCD2 nuclear foci. BRCA2 interacts with RAD51, and these proteins are required for homology-directed DNA repair (HDR). Disruption of genes in this pathway results in chromosome instability, cellular hypersensitivity to DNA cross-linking agents, and a propensity to cancer progression.

observed in *Brca2* hypomorphic mice (Tutt et al. 2001; McAllister et al. 2002). Taken together, the phenotype of the *Fancd2*-deficient mice provides an important experimental verification of the sequence of molecular events in the FA pathway (Fig. 1), with *Fancd2* and *Brca2*/*Fancd1* playing a more critical downstream role.

Role of the FA/BRCA pathway in homologous recombination repair

Increasing evidence supports a role for the FA/BRCA pathway in HDR. First, FA cells are hypersensitive to DNA cross-linking agents, similar to the cellular phenotype observed in HDR-defective CHO cells containing mutations in the DNA recombination genes *XRCC3* (Pierce et al. 1999) or *BRCA2* (Kraakman-van der Zwet et al. 2002). Second, activated (monoubiquitinated) FANCD2 forms nuclear foci with BRCA1 and RAD51 during S phase, a cell-cycle stage in which HDR between sister chromatids is known to occur (Taniguchi et al. 2002). Third, FA cells exhibit an increased mutation frequency, based on the high number of spontaneous mutations observed in the reporter gene, *HPGRT* gene. Moreover, the abnormal spectrum of *HPGRT* mutations observed in FA cells is consistent with abnormal HDR (Papadopoulos et al. 1990). Finally, the BLM helicase, another protein identified as a component of the FA complex (A/C/E/F/G complex; Meetei et al. 2003), has been implicated in HDR activities such as telomere length maintenance (Stavropoulos et al. 2002). Although BLM is not required for the monoubiquitination of FANCD2, its presence in the complex suggests that BLM may recruit the FA complex to chromatin.

Analysis of the new *Fancd2*-deficient mice provides additional clues to the function of the FA pathway in HDR (Houghtaling et al. 2003). Spermatocytes isolated from the *Fancd2*-deficient mice exhibited abnormal pair-

ing of homologous chromosomes during the meiotic pachytene stage. Similarly, somatic cells isolated from these mice exhibited spontaneous and DNA damage-inducible chromosome quadriradial forms, composed of mispaired nonhomologous chromosomes. These observations raise the interesting possibility that the FA/BRCA pathway regulates the fidelity of homologous chromosome or sister chromatid pairing, whereas the downstream BRCA2/RAD51 elements mediate the more direct events in HDR. Consistent with this view, human FA fibroblasts which have biallelic mutations in an upstream FA gene, such as FANCA or FANCG, have only a minor (twofold) defect in HDR (A. D'Andrea, unpubl.), compared with the eightfold defect observed in *BRCA1*^{-/-} cells (Moynahan et al. 1999) and *BRCA2*^{-/-} cells (Moynahan et al. 2001).

Several questions regarding the role of the FA/BRCA pathway in HDR remain unanswered. Are *Fancd2*-deficient MEF or ES cells specifically defective in HDR? Are other DNA repair mechanisms also defective? A systematic analysis of *Fancd2*-deficient cells, using plasmid-based recombination substrates, will be a logical starting point for addressing these questions (Pierce et al. 1999; Tutt et al. 2001).

Another critical unanswered question is the molecular basis of the selective DNA cross-linker sensitivity of *Fancd2*-deficient cells. In general, FA cells are hypersensitive to MMC but exhibit normal resistance to ionizing radiation (IR). Both MMC and IR generate double-strand DNA breaks (dsbs; D'Andrea and Grompe 2003), lesions normally repaired either by HDR or nonhomologous end joining (NHEJ). The selective defect in MMC cross-link repair in FA cells suggests a defect in the ability to sense DNA cross-links or to process cross-links into dsbs. On the one hand, the FA protein complex may function to sense DNA damage. For instance, the FA complex, containing the BLM helicase component, may detect and bind to a DNA cross-link, leading to activation of

FANCD2 monoubiquitination and a subsequent repair process (Fig. 1). On the other hand, the FA pathway may function further downstream to process the DNA damage. The monoubiquitinated FANCD2 protein may cooperate with BRCA2 and RAD51 to repair DNA containing cross-links. Despite the rapid progress in the FA/BRCA field, including gene cloning, the elucidation of biochemical events in the pathway, and successful mouse modeling, no consistent explanation has yet emerged for the selective cross-linker hypersensitivity of FA cells.

Disruption of the FA/BRCA pathway during epithelial cancer progression

The most important finding of Houghtaling et al. (2003) is the predisposition of *Fancd2*-deficient mice to epithelial cancers—mainly breast, ovarian, and liver cancers. Human cancers are usually epithelial in origin, and develop with advancing age. Human tumors often display complex cytogenetic profiles, including aneuploidy and chromosome structural abnormalities. As most genetic murine models described to date develop soft tissue sarcomas and lymphomas, these models bear little relevance to the common epithelial cancers of humans. The new *Fancd2*-deficient murine model, along with the *Brca2*-deficient model (McAllister et al. 2002) and the telomerase-deficient model (Artandi et al. 2000) which also develop epithelial cancers, may therefore be more relevant to the study of many human cancers.

The development of epithelial cancers in the *Fancd2*-deficient mice has several important implications. First, the findings strongly support a genetic interaction between *Fancd2* and *Brca2*, consistent with the pathway described in Figure 1. Biochemical evidence further supports this genetic interaction, as the activated (monoubiquitinated) form of FANCD2 colocalizes with BRCA2 in chromatin, and a biochemical complex containing these proteins has been partially purified (A. D'Andrea, unpubl.).

Second, the findings suggest a possible interaction between the FA/BRCA pathway and telomere length maintenance. Consistent with this notion, FA cells have accelerated telomere shortening (Callen et al. 2002). Future studies, such as the crossing of *Fanc*-deficient and telomerase-deficient mice, are needed to determine whether activated FANCD2 functions to maintain telomere length, perhaps via HDR. Loss of telomerase activity or loss of activated FANCD2 protein may contribute to telomere attrition, end-to-end chromosome fusion, and epithelial carcinogenesis.

Third, the gradual progression of epithelial cancers in the *Fancd2*-deficient mice will allow the systematic assessment of relevant chromosome breaks, deletions, and insertions in the tumors. In this way, the development of the murine epithelial cancers may mimic epithelial cancer progression in humans. Tumor cell lines derived from the *Fancd2*-deficient mice should be examined by spectral karyotype analysis (SKY), in order to determine the frequency of site-specific chromosome translocations and amplifications. Tumor-derived genomic DNA should be analyzed by array comparative genomic hy-

bridization (O'Hagan et al. 2002), to detect amplifications and deletions of cancer-relevant loci, specifically in regions syntenic to human epithelial cancer hotspots.

The *Fancd2*-deficient mice may elucidate other aspects of epithelial cancer development. The generation of *Fancd2*^{-/-}, *p53*^{-/-} double-knockout mice will allow the assessment of a genetic interaction between the FA/BRCA pathway and *p53*. Perhaps the double-knockout mice will have enhanced tumorigenesis, with shortened tumor latency and a different tumor spectrum. Similarly, it will be important to determine whether restoration of the FA pathway, perhaps by compensatory mutations, results during the progression of epithelial cancer in these animals. Recent studies indicate that tumors from FA patients may result, at least in part, from somatic reversion, restoration of the FA pathway, and restoration of genomic stability and drug resistance (Ikeda et al. 2003).

In addition to Houghtaling et al. (2003), other recent studies support a pivotal role of the FA/BRCA pathway in epithelial cancer progression. Taniguchi et al. (2003) demonstrated that at least 18% of primary ovarian epithelial cancers have a disruption of the FA/BRCA pathway, perhaps accounting for the well known chromosome instability and cisplatin hypersensitivity of these tumors. Disruption of the pathway results from the methylation and silencing of one of the upstream FA genes, *FANCF*. Also, Van Der Heijden et al. (2003) recently suggested that germline *FANCG* or *FANCC* mutations may account for the chromosome instability and cross-linker sensitivity of tumors from some patients with inherited pancreatic cancer. Tumors from such patients are hemizygous for *FANCG*; they contain an inherited (mutant) *FANCG* allele, whereas the wild-type allele has been deleted.

These studies indicate that disruption of the FA/BRCA pathway, by germline mutations, somatic mutations, or epigenetic silencing of *FANC* genes, may contribute to epithelial cancer progression. Transient inactivation of the FA/BRCA pathway may result in chromosome instability, the activation of new oncogenes, and the inactivation of tumor suppressors, thus enhancing the malignant phenotype. Restoration of the FA/BRCA pathway, by compensatory mutations later in the evolution of the cancer, may restore genomic stability, may provide an alternative mechanism for telomere length maintenance (ALT), and may promote chemotherapy resistance. The new finding of epithelial cancers in *Fancd2*-deficient mice will no doubt fuel new efforts to examine the integrity of the FA/BRCA pathway in other human cancers, especially those cancers with chromosome breakage and DNA cross-linker hypersensitivity.

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