BRCA1: A Missing Link in the Fanconi Anemia/BRCA Pathway

Alan D. D’Andrea

Summary: Domchek and colleagues provide a case report of a 28-year-old woman with congenital abnormalities, inherited ovarian cancer, and carboplatin hypersensitivity. Interestingly, the woman had validated germline mutations in both BRCA1 alleles. These findings further implicate BRCA1 in the Fanconi anemia/BRCA pathway and have important implications for BRCA1 genetic testing.

See related article by Domchek et al., p. 399 (6).

Significant advances in our understanding of breast and ovarian cancer have resulted from the genetic linkage mapping and cloning of 2 major tumor suppressor genes, BRCA1 and BRCA2. Mutations in BRCA1 and BRCA2 account for approximately 16% of the familial risk of breast cancer (1). Moreover, heterozygous carriers of mutations in BRCA1 and BRCA2 have an 82% lifetime risk of breast cancer and a 54% and 23% risk of ovarian cancer, respectively (2). Biallelic germline mutations in BRCA2 account for a rare and highly cancer-prone subtype of Fanconi anemia (3); however, humans with validated biallelic germline mutations in BRCA1 have not been identified, suggesting that at least one functional allele of BRCA1 is required for human embryogenesis and development.

Fanconi anemia is an autosomal-recessive or X-linked-recessive genetic disease characterized by multiple congenital anomalies, bone marrow failure, cancer predisposition, and cellular hypersensitivity to DNA cross-linking agents, such as mitomycin C and cisplatin. There are 15 known Fanconi anemia genes, and the encoded 15 Fanconi anemia proteins (Fig. 1, green) cooperate in a common pathway, the so-called Fanconi anemia/BRCA pathway (4), which is required for the repair of DNA cross-links (ref. 5; Fig. 1). Additional proteins (shown in red in Fig. 1) such as BRCA1, while not bona fide Fanconi anemia proteins (i.e., not encoded by genes known to have germline mutations in patients with Fanconi anemia), are also required for the activity of the pathway and are therefore candidate Fanconi anemia proteins. Interestingly, at least 4 of the Fanconi anemia genes, FANCD1/BRA2, FANCN/PALB2, FANCl/BRIP1, and FANCO/RAD5IC, are also breast/ovarian cancer susceptibility genes. Heterozygote carriers of germline mutations in these genes carry an increased cancer risk, albeit at highly variable penetrance. A new study by Domchek and colleagues (6) shows that the BRCA1 protein is also a critical component of this pathway and that BRCA1 may itself be a Fanconi anemia gene.

The interaction of BRCA1 with other proteins in the Fanconi anemia pathway has been suspected for several years. BRCA1, like the bona fide Fanconi anemia proteins, has a well-known function in the maintenance of genomic stability through homologous recombination repair and in the promotion of DNA repair of interstrand cross-links (7). Moreover, knockdown of BRCA1 in tumor cells results in a reduction of FANCD2 monoubiquitination and nuclear FANCD2 DNA repair foci (8), suggesting that BRCA1 is an amplifier of the Fanconi anemia/BRCA pathway. Perhaps most interestingly, BRCA1 is a component of a large nuclear protein complex (Fig. 1) consisting of at least 3 other bona fide Fanconi anemia proteins, BRCA2 (FANCD1), PALB2 (FANCN), and BRIP1 (FANCJ). PALB2 was originally identified in a screen of BRCA2-binding proteins (9), and it binds to the extreme N-terminus of BRCA2. PALB2 also binds to the C-terminal BCRT repeats of BRCA1, and BRCA1, in turn, binds directly to BRIP1 (J; Fig. 1). This intimate interaction of BRCA1 with other bona fide Fanconi anemia proteins, which are themselves breast/ovarian cancer susceptibility proteins, further suggests that BRCA1 directly participates in the Fanconi anemia/BRCA pathway and that biallelic BRCA1 mutations might result in Fanconi anemia or a Fanconi anemia-like syndrome.

Indeed, in their case report, Domchek and colleagues (6) determined that the proband with ovarian cancer had biallelic mutations in BRCA1. Although one mutant allele was clearly deleterious (the known c.2457delC allele), the other allele was a variant of unknown significance (VUS), encoding a BRCA1 protein with a V1736A amino acid substitution. The authors provide several lines of reasoning to determine that this VUS allele is also deleterious and encodes a dysfunctional BRCA1 protein. First, they examined other kindreds that carry this BRCA1 variant allele. These kindreds have family members with breast and ovarian cancer, and the combined OR in favor of the variant allele being pathogenic was elevated (ratio of 234:1). Second, the V1736A mutation falls in one of the C-terminal BRCT domains of BRCA1. Although the mutation did not directly disrupt the BRCT-binding surface of BRCA1, it indirectly altered the binding affinity of the BRCT domain for
The breast was palpable (but not visible) in the left axilla, and the skin overlying the tumor was dimpled. Spontaneous regression occurred 6 months after diagnosis. The patient underwent four cycles of primary chemotherapy, followed by a planned interval of 6 months without treatment for assessment before proceeding to adjuvant therapy. However, the patient developed local recurrence after 6 months. She then received four cycles of polychemotherapy, and the tumor responded. After a period of 12 months without treatment, the patient was referred for assessment for liver metastases, which were present. A liver resection was performed. After a period of 3 months, a new liver lesion was detected and the patient was referred to a medical oncologist for further management.

In summary, this important new work by Domchek and colleagues (6) identifies a new autosomal recessive genetic syndrome (developmental defects, inherited ovarian cancer susceptibility, and cross-linker hypersensitivity caused by biallelic mutations in BRCA1). The work also describes a
systematic approach for testing variant BRCA1 proteins for functional activity in vitro. As more variant BRCA1 alleles are identified through expanding genome-sequencing efforts, there will be a growing need for better functional assays to distinguish deleterious from benign variants.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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REFERENCES

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