

D-Day for BRCA2

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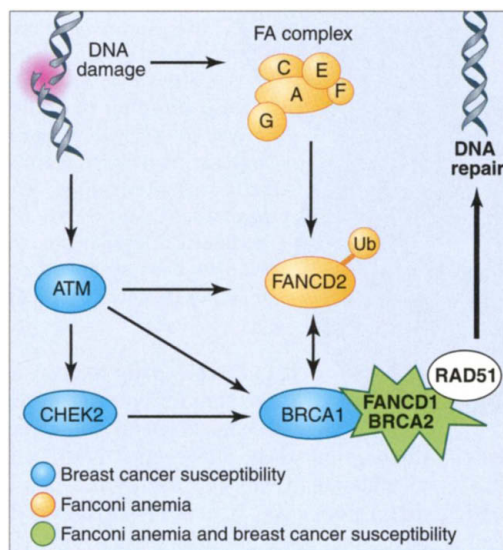
Important discoveries are sometimes so neat and satisfying that, in retrospect, they seem obvious. So it is with the finding described by Howlett *et al.* (1) on page 606 of this issue. These authors disclose that the inheritance of two defective copies of the *BRCA2* breast cancer susceptibility gene (2) can lead to Fanconi anemia (FA) (3), a complex disorder characterized by congenital abnormalities, progressive bone marrow failure, and cancer susceptibility.

Heterozygous carriers of *BRCA2* mutations inherit a high risk of developing breast cancer (up to 85%) and other cancers such as ovarian and pancreatic. No developmental or other obvious defects have been noted in these individuals. The *BRCA2* protein is thought to be important in the repair of DNA damage by homologous recombination, at least in part by regulating the activity of RAD51 (2). Cells lacking *BRCA2* inaccurately repair damaged DNA, leading to gene mutation and progression of tumors, and are particularly sensitive to DNA cross-linking agents.

Most patients with FA present within the first decade of life with bone marrow failure and cancer, typically acute myeloid leukemia and squamous cell carcinoma, usually of the head and neck (3). This is accompanied by congenital abnormalities such as growth retardation and skeletal defects (microcephaly and absent radii or thumbs), kidney defects, and abnormal skin pigmentation. The heterogeneity of the disease leads to difficulties in making a firm clinical diagnosis, and therefore the cellular hypersensitivity to DNA cross-linking agents such as mitomycin C that these patients exhibit is used as the gold standard diagnostic tool.

FA is a recessively inherited disorder that can result from mutation in at least eight individual genes (3). Apart from genes B and D1, these have all been isolated previously and encode diverse proteins, many of which interact within a cellular complex related to the maintenance of genomic stability.

Howlett *et al.* (1) show that one of the previously unidentified FA genes, *FANCD1*, is in fact *BRCA2*. The cellular consequences of homozygosity for *BRCA2* mutation—spontaneous chromosome instability and hypersensitivity to DNA cross-linking agents—are similar to those in cells derived from FA pa-



DNA repair proteins implicated in Fanconi anemia and breast cancer susceptibility. The Fanconi anemia proteins are thought to be present in the nucleus as a complex. ATM can phosphorylate FANCD2, BRCA1, and CHEK2. FANCD2 can interact with BRCA1 and may be a substrate for its ubiquitin ligase activity. FANCD1/BRCA2 is thought to lie downstream of FANCD2 and can associate with BRCA1. BRCA2 binds RAD51, which is involved in repair of damaged DNA. Heterozygosity for *BRCA1*, *BRCA2*, *ATM*, and *CHEK2* has been implicated in breast cancer susceptibility (2, 8, 10). Homozygosity for *FANCD1* and *BRCA2* genes causes Fanconi anemia (1, 3).

tients. This prompted the authors to determine the sequence of the *BRCA2* gene in *FANCD1* patients. One individual with FA carried two different truncating mutations in *BRCA2* typical of those that cause susceptibility to breast cancer when heterozygous. Individuals carrying two *BRCA2* mutations have not been reported before, and this result was surprising as it was thought likely that this combination of mutations would be lethal. An explanation for this finding might be suggested, however, by previous work on *BRCA2* knockout mice. Mice homozygous for mutations that eliminate most of the *BRCA2* gene do die early in embryogenesis, whereas those with apparently milder ("hypomorphic") mutations can survive to adulthood (4, 5). It is intriguing that these mice have some phenotypes that are reminiscent of FA, including small gonads, skeletal defects, and sensitivity to DNA cross-linking agents (4, 5). It is possible therefore that only hypomorphic *BRCA2* mutations lead to FA, whereas stronger mutations are lethal during embryogenesis. The final piece of evidence implicating *BRCA2* in the patho-

genesis of FA is the partial rescue of sensitivity to mitomycin C of a *FANCD1* cell line by introduction of a wild-type *BRCA2* gene (1). Although this result, in itself, is open to alternative interpretation, taken together with the genetic data, it provides a persuasive argument for the role of *BRCA2* mutation in FA.

Preliminary evidence is also presented by the authors for a role of *BRCA2* mutation in another FA complementation group, *FANCB*, although this requires additional confirmation.

This is not the first link between FA and breast cancer susceptibility. Another FA complementation group protein, *FANCD2*, can interact and colocalize with *BRCA1* (6). Moreover, both *FANCD2* protein and *BRCA1* can be phosphorylated by ATM, itself recently implicated in susceptibility to breast cancer (7, 8). Thus, it seems that the pathways disrupted in FA and breast cancer susceptibility are intimately connected on several levels (see the figure).

So if *BRCA2* can be an FA gene, could other FA genes be new *BRCA* genes? Little evidence could be found in previous studies for an excess of cancers in relatives of FA patients (9). Nevertheless, this work could not take into account the existence of multiple genes for FA; if only some behaved like *BRCA2*, the analysis would be negative. It would be particularly interesting to examine *FANCD2*, with what appears to be a central role in the pathway (see the figure). Doubtless the new work by Howlett *et al.* (1) will stimulate considerable interest in readdressing the issue of cancer susceptibility in FA heterozygotes.

Only a small proportion of the cases of FA, which in itself is rare, is caused by *BRCA2* mutation. But the importance of this finding is that it connects two previously different bodies of work on DNA repair. Doubtless this will fuel progress into understanding both breast cancer and FA.

References

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