Homologous Recombination as a Safeguard Against Tumorigenesis

BRCA1 and *BRCA2* mutations are estimated to be responsible for 80 percent of familial breast cancers and more than 95 percent of familial ovarian cancers. The discovery of these ovarian cancer genes was met with great excitement and hope that the etiology of these diseases would be understood. Although great progress has been made toward the understanding of the function of these proteins, a full understanding has eluded investigators. The protein products of both of these genes are quite large: 1863 amino acids for *BRCA1* and 3418 amino acids for *BRCA2*. They exhibit no significant homology with each other, and there are no clear homologs identified in easily manipulated model organisms, such as yeast. The mouse homologs of *BRCA1* and *BRCA2* (Brca1 and Brca2) share 58 percent and 59 percent identity with their human counterparts, respectively. A wide spectrum of mutations has been identified in both genes, including both truncating and missense mutations.

The evidence that *BRCA1* and *BRCA2* are involved in DNA repair, in particular homologous recombination, is substantial. Both proteins co-localize with Rad51 to nuclear foci following DNA damage. Although clearly a direct interaction for *BRCA2,* the association of *BRCA1* with Rad51 is likely to be indirect, perhaps mediated by *BRCA2*. In *BRCA1,* a less-defined region for Rad51 interaction has been mapped to a region encoded by the large exon 11. In addition to changes in nuclear localization upon DNA damage, *BRCA1* also undergoes changes in phosphorylation. Further evidence that *BRCA1* and *BRCA2* are involved in DNA repair comes from the sensitivity of cell lines deficient in these proteins to DNA-damaging agents, including those agents that cause double-strand breaks (DSBs), such as ionizing radiation.

Direct Evidence for a Role for BRCA1 in Homologous Recombination

Sensitivity to ionizing radiation is compelling evidence that *BRCA1*- and *BRCA2*-deficient cells are defective in repair of DSBs. As discussed above, 2 separate pathways play major roles in DSB repair in mammalian cells (homology-directed repair and nonhomologous repair), and ionizing radiation-sensitive cell lines have been characterized with defects in both repair pathways. We examined DSB repair in a Brca1-deficient mouse embryonic stem (ES) cell line (Moynahan et al. Molecular Cell. 1999). Whereas nonhomologous repair of DSBs is intact in these cells, homology-directed repair is significantly impaired. Homologous integration of transfected DNA is also reduced. Since these ES cells contain the exon 11 deletion found in mice that conditionally develop mammary gland tumors, the homologous repair defect is, thus far, found to correlate with tumorigenesis.

Moynahan ME, Chiu JW, Koller BH, Jasin M. 1999 Brca1 controls homology-directed DNA repair. Mol Cell. 1999;4:511-518.

Jasin M. 2000 Chromosome breaks and genomic instability. Cancer Invest. 2000;18:78-86.

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