Recombination Proteins: Rad51-related and Rad51-associated Proteins

The discovery of a major role for homologous recombination as a DNA repair pathway implied that cell mutants, isolated on the basis of sensitivity to certain DNA-damaging agents, could have homologous repair defects. We tested candidate cell mutants and determined that 2 of them have substantially reduced levels of homologous repair of double-strand breaks, although nonhomologous repair is intact (Johnson et al. Nature. 1999; Pierce et al. Genes Dev. 1999).

As these cell mutants demonstrate a high frequency of spontaneous chromatid breaks and other types of aberrations, homologous repair is thus directly implicated in the maintenance of genomic integrity, even in the absence of exogenous DNA-damaging agents. This raises an important question regarding the sources of spontaneous damage. These 2 cell mutants are deficient in XRCC2 and XRCC3, proteins which have limited sequence homology to Rad51 in the nucleotide-binding motif.

Multiple protein interactions have been demonstrated for the mammalian Rad51 protein. Many of these interactions are presumably direct, being demonstrated by 2-hybrid or direct physical analyses. This includes an interaction of Rad51 with the XRCC3 protein. Unlike XRCC3, the XRCC2 protein does not directly interact with Rad51, but may interact indirectly through other proteins. In addition to XRCC2 and XRCC3, 3 other proteins share homology to Rad51 in the nucleotide-binding motif: Rad51B, Rad51C, and Rad51D. XRCC2 may interact with Rad51 through its interaction with Rad51D, since Rad51D interacts with a postulated Rad51C/B heterodimer.

Although their role in promoting recombination is unknown, it has been postulated that this group of 5 Rad51-related proteins (XRCC2, XRCC3, and Rad51B-D) may function similarly to the yeast Rad51-

related proteins, Rad55, and Rad57. These proteins, which interact with yeast Rad51, promote the DNA strand exchange activity of Rad51 *in vitro.* Other proteins that interact with Rad51 include Rad52, Rad54, and RPA, and, as discussed in the next project listed, the products of the hereditary breast cancer genes *BRCA1* and *BRCA2.*

Liang F, Romanienko PJ, Weaver DT, Jeggo PA, Jasin M. 1996 Chromosomal double-strand break repair in Ku80-deficient cells. Proc Natl Acad Sci USA. 1996:93:8929-8933.

Johnson RD, Liu N, Jasin M. 1999 Mammalian XRCC2 promotes the repair of DNA double-strand breaks by homologous recombination. Nature. 1999;401:397-399.

Pierce AJ, Johnson RD, Thompson LH, Jasin M. 1999 XRCC3 promotes homology-directed repair of DNA damage in mammalian cells. Genes Dev. 1999;13:2633-2638.

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