mlh3 mutations in baker’s yeast alter meiotic recombination outcomes by increasing noncrossover events genome-wide

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Abstract

Mlh1-Mlh3 is an endonuclease hypothesized to act in meiosis to resolve double Holliday junctions into crossovers. It also plays a minor role in eukaryotic DNA mismatch repair (MMR). To understand how Mlh1-Mlh3 functions in both meiosis and MMR, we analyzed in baker’s yeast 60 new mlh3 alleles. Five alleles specifically disrupted MMR, whereas one (mlh3-32) specifically disrupted meiotic crossing over. Mlh1-mlh3 representatives for each class were purified and characterized. Both Mlh1-mlh3-32 (MMR+, crossover-) and Mlh1- mlh3-45 (MMR-, crossover+) displayed wild-type endonuclease activities in vitro. Msh2- Msh3, an MSH complex that acts with Mlh1-Mlh3 in MMR, stimulated the endonuclease activity of Mlh1-mlh3-32 but not Mlh1-mlh3-45, suggesting that Mlh1-mlh3-45 is defective in MSH interactions. Whole genome recombination maps were constructed for wild-type and MMR+ crossover-, MMR- crossover+, endonuclease defective and null mlh3 mutants in an S288c/YJM789 hybrid background. Compared to wild-type, all of the mlh3 mutants showed increases in the number of noncrossover events, consistent with recombination intermediates being resolved through alternative recombination pathways. Our observations provide a structure-function map for Mlh3 that reveals the importance of protein-protein interactions in regulating Mlh1-Mlh3’s enzymatic activity. They also illustrate how defective meiotic components can alter the fate of meiotic recombination intermediates, providing new insights for how meiotic recombination pathways are regulated.

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