2018 LPS BMCB Best Paper Award: Najla Al-Sweel

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

Najla Al-Sweel[1], Vandana Raghavan[1], Abhishek Dutta[2], V. P. Ajith[2], Luigi Di Vietro[3¤], Nabila Khondakar[1], Carol M. Manhart[1], Jennifer A. Surtees[4], K. T. Nishant[2,5]*, Eric Alani[1]*

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 intermedi- ates 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 com- ponents can alter the fate of meiotic recombination intermediates, providing new insights for how meiotic recombination pathways are regulated.

PLOS Genetics | https://doi.org/10.1371/journal.pgen.1006974 August 21, 2017