MLH1, one of four MutL homologs in S. cerevisiae, is involved in mismatch repair during mitosis and meiosis and plays a role separate from its mismatch repair functions in crossing-over during meiotic recombination. Mlh1p is involved in the repair of mismatches caused by errors during replicationas well as the repair of DNA damage caused by cisplatin, alkylating agents, and oxidation. Mlh1p is also involved in the correction of mismatches that arise during the formation of heteroduplex DNA between two homologous chromosomes during meiotic recombination. Failure to repair these mismatches during meiosis leads to an increase of post-meiotic segregationevents in which the 4:4 Mendelian segregation pattern of the 8 single-strands of DNA is altered to a 5:3 non-Mendelian segregation pattern. Consistent with its multiple roles in mismatch repair, an mlh1 mutant displays a severe mutator phenotype as well as an increase in PMS events. An increase in Mlh1p levels also displays a mutator phenotype. In addition to its role in mismatch repair, Mlh1p has been proposed to be involved in regulating the total level, types, and resolution of heteroduplexes during meiotic crossing-over.The functional specificity of Mlh1p may result from its interaction with each of the three other MutL homologs. The Mlh1p-Pms1p heterodimer plays a major role in mismatch repair but a limited role in meiotic crossing-over. Although the Mlh1p-Pms1p heterodimer does not bind mismatched DNA, it interacts with both Msh2p-Msh3p and Msh2-Msh6p heterodimers during mismatch repair. A pms1 mutant exhibits a severe mutator phenotype and increased PMS events but normal levels of crossing-over. In contrast to the Mlh1p-Pms1p heterodimer, Mlh1p-Mlh2p and Mlh1p-Mlh3p heterodimers play smaller roles in general mismatch repair and larger roles in the resolution of heteroduplexes formed during meiotic recombination. The Mlh1p-Mlh2p and Mlh1p-Mlh3p heterodimers are involved in the repair of specific types of mismatches. Both mlh2 and mlh3 single mutants display defects in both the levels and types of cross-over events observed during meiosis. An mlh3 mutant displays a reduced level of crossing-over during meiosis similar to an mlh1 single mutant, an msh4 single mutant, and an mlh1 msh4 double mutant, suggesting that the Mlh1p-Mlh3p heterodimer may interact with the Msh4p-Msh5p heterodimer to regulate cross-overs.Transcription of MLH1 does not appear to be regulated during the mitotic and meiotic cell cycles.Mlh1p is similar to the bacterial MutL and HexB mismatch repair proteins and the human hMLH1 proteinresponsible for hereditary non-polyposis colorectal cancer. Mutating MLH1 at positions analogous to those observed to be associated with HNPCC in humans with mutated hMLH1 results in a mutator phenotype in yeast.