The Archaeal origin of eukaryotic nuclear mismatch repair

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During DNA synthesis and homologous recombination the resulting double-stranded DNA will occasionally have mismatched bases, which are corrected by the mismatch repair (MMR) system. Mismatches are repaired by coordinated actions between the mutS and mutL enzymes in Bacteria, Archaea, and eukaryotes. The eukaryotic MMR system is composed by mutS homologs MSH1-6 and mutL homologs MLH1-4. MSH1 homologs are targeted to mitochondria or chloroplasts; MSH2,3,6 carry out nuclear MMR; meiosis-specific MSH4 and MSH5 stabilize double Holliday junctions. MLH1 participates in nuclear MMR with MLH2 and MLH4 (PMS1-2), while in meiosis it interacts with MLH3 to resolve crossover. Previously, an endosymbiotic origin of the eukaryotic MMR was proposed by Lin et al. (2007), suggesting an important mitochondrial contribution to nuclear eukaryotic DNA metabolism and meiosis. This would suggest that canonical meiosis must have evolved after the acquisition and establishment of the mitochondrion in an eukaryotic ancestor. We searched for homologues of mutS and mutL in Bacteria, Archaea, and Eukarya, and applied sophisticated methods to reconstruct their phylogenetic relationships. Our results demonstrate that eukaryotes acquired the MMR system vertically, inheriting it from an Archaeal ancestor. Those ancestral genes were further duplicated in the eukaryotic ancestor and are responsible for nuclear processes including meiosis. Additionally, some MMR genes were acquired during the endosymbiotic origins of mitochondria and chloroplasts. Regarding mutS, all three sources can still be traced in eukaryotes: the nuclear paralogs have Asgard Archaea origin; the mitochondrial and chloroplastic homologs have alphaproteobacterial and cyanobacterial origins respectively. Regarding mutL only the ancestral nuclear and chloroplastic homologs can be detected, suggesting that the mitochondrial form was lost or replaced in extant eukaryotes. In general there is no obvious mitochondrial contribution to nuclear DNA metabolism and meiosis systems and the previously proposed role of mitochondria in the evolution of meiosis was overestimated.