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Oxidative damage and the DNA glycosylase MutYH

av

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Oxidative damage and the DNA glycosylase MutYH

Abstract

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The DNA glycosylase MutYH is highly conserved throughout evolution, and homologs are found in most eukaryotes and prokaryotes examined. MutYH functions as a base excision repair DNA glycosylase that excises adenines misincorporated opposite 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxoG), one of the most stable products of oxidative DNA damage. Germline mutations in *MutYH* in humans predispose to *MutYH*-associated polyposis (MAP), characterised by multiple colorectal adenomas and carcinomas. Oxidative stress and susceptibility to carcinogenesis involve additional pathways, such as the glutathione/glutathione S-transferase detoxification system. The role of the base excision repair enzyme MutYH in DNA damage repair and checkpoint control in fission yeast is here shown not to be restricted to oxidative damage.

The fission yeast gene encoding MutYH, *myh1*$^+$ displays a strong interaction with the checkpoint gene *rad1*$^+$. UV irradiation of *myh1 rad1* double mutants results in severe chromosome segregation defects and visible DNA fragmentation, and a failure to activate the checkpoint. The *myh1 rad1* double mutants furthermore display hypersensitivity to genotoxic compounds MMS and HU. Additionally, *myh1 rad1* double mutants exhibit morphological defects in the absence of DNA damaging agents.

Fission yeast MutYH (Myh1) has a role in DNA repair after treatment with DNA crosslinking and strand-breaking chemotherapeutic agents. Myh1 contributes to survival upon genotoxic stress, particularly in a *rad1* mutant background, and relocalises to the nucleus after exposure to the DNA crosslinking agent cisplatin or following oxidative stress. An asymmetric function of the 9-1-1 checkpoint sensor complex is conceivable in MutYH-mediated base excision repair, and further extends the view of MutYH function in DNA damage checkpoint control and DNA repair.

Phylogenetic distribution and sequence analysis of the MutY, MutM, and MutT homologs, enzymes involved in repair of 8-oxoG, indicate highly conserved protein domains and evolutionary loss of individual 8-oxoG repair components, predominantly within the fungal domain of eukaryotic life. The MutM homolog is the most prevalent 8-oxoG repair enzyme among eukaryotes. This likely indicates the MutM component as the major repair enzyme in removal of 8-oxoG damage.

S. cerevisiae mutants lacking glutathione S-transferases (GSTs) display a number of phenotypic defects under different stress conditions. The phenotypes of single and multiple mutants defective in GSTs, exposed to oxidants and other toxic agents, indicate the importance of yeast GSTs in protection against oxidative stress. A complex relationship most likely exists between different GSTs in general protection against oxidative stress and in specific protein redox regulation.

Keywords: Oxidative damage, 8-oxo-7,8-dihydro-2′-deoxyguanosine, Base excision repair, DNA glycosylase, Mismatch repair, DNA damage checkpoint, 9-1-1 complex, Glutathione-S-transferases, Colon cancer.
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