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Review

MutY-glycosylase: An overview on mutagenesis and activities beyond the GO system

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ABSTRACT

MutY is a glycosylase known for its role in DNA base excision repair (BER). It is critically important in the prevention of DNA mutations derived from 7,8-dihydro-8-oxoguanine (8-oxoG), which are the major lesions resulting from guanine oxidation. MutY has been described as a DNA repair enzyme in the GO system responsible for removing adenine residues misincorporated in 8-oxoG:A mispairs, avoiding G:C to T:A mutations. Further studies have shown that this enzyme binds to other mispairs, interacts with several enzymes, avoids different transversions/transitions in DNA, and is involved in different repair pathways. Additional activities have been reported for MutY, such as the repair of replication errors in newly synthesized DNA strands through its glycosylase activity. Moreover, MutY is a highly conserved enzyme present in several prokaryotic and eukaryotic organisms. MutY defects are associated with a hereditary colorectal cancer syndrome termed MUTYH-associated polyposis (MAP). Here, we have reviewed the roles of MutY in the repair of mispaired bases in DNA as well as its activities beyond the GO system.

Contents

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1. Introduction

One of the most abundant and highly mutagenic oxidized DNA lesions is 8-oxo-7,8-dihydroguanine (8-oxoG or GO). This lesion can form a canonical base pair with cytosine or mispair with adenine, inducing G:C to T:A transversions [1]. MutY is one of the main enzymes involved in defending against the mutagenic effects of 8-oxoG lesions [2]. MutY is a DNA glycosylase that is a member of the GO repair system. MutY is responsible for removing adenines misincorporated opposite GO or G; therefore, it reduces G:C to T:A transversions [3]. In this sense, MutY was first reported in a study conducted by Nghiem et al. [1] where the authors described the *mutY* gene as a mutator locus related to an increase in the occurrence of G:C to T:A transversions in *Escherichia coli*. The mispairs repaired by MutY were described by Au et al. [4]. In this work, the MutY enzyme was purified, and the repair pathway of the A:G mismatch pair was reconstituted. It was demonstrated that the *mutY* gene encodes an adenine glycosylase whose activity may occur independently of DNA methylation [4]. The following studies demonstrated the ability of MutY to repair adenine mispairings to both cytosine and 5-hydroxyuracil (hoU) [5,6]. Other studies have described MutY as responsible for guanine repair from 8-oxoG:G mispairings *in vitro* at reduced rates [7,8]. Interestingly, MutY has an important and particular feature; it is the only glycosylase described thus far that is able to perform excision of an undamaged base from DNA [2,9]. Initially, MutY believed to be directed to newly synthesized DNA strands to excise the undamaged base to avoid the transversions that arise from DNA replication in the presence of 8-oxoG [10]. However, subsequent studies have shown that MutY is involved in the mechanisms responsible for mutations in methylated DNA strands; this is discussed in Section 5 of this review.

Bioinformatics analysis demonstrated that a correlation exists between the presence or the absence of the *mutY* gene and the G:C content in genomes in several prokaryotic organisms [11]. A higher G:C content in genomes is associated with the presence of *mutY*; organisms with a high A:T content in their genomes tend to lack the *mutY* gene [11]. This bioinformatics study is consistent with the idea that MutY plays a role in DNA repair that prevents G:C to T:A mutations. As a highly conserved enzyme, MutY is also present in eukaryotes [12]. MutY human homologue (MUTYH) alterations in its activity are associated with a hereditary colorectal cancer syndrome termed MUTYH-associated polyposis (MAP) [9].

Here, we review the role of MutY in DNA repair as well as its activities beyond the GO system. MutY interacts with proteic complexes involved in the maintenance of genome integrity and in this way avoids the release of harmful repair intermediates into cells.

2. MutY × MUTYH

The GO repair system is found in organisms ranging from *E. coli* to humans [13,14]. However, only the MutY enzyme presents as a conserved sequence between prokaryotes and eukaryotes [12]. MUTYH shares 41% sequence similarity to its *E. coli* counterpart and 79% homology to its mouse homologue (mMYH) [12]. Despite this homology, MUTYH is 21 kDa larger than MutY (60 kDa and 39 kDa, respectively); the additional sequence encodes for structural domains related to specific interactions between MUTYH and the enzymes involved in long patch base excision repair (BER), DNA replication, mismatch repair (MMR), and cell cycle checkpoints [15,16]. In this context, Xie et al. [17] used mouse embryonic fibroblast cell lines deficient in MYH and OGG1 genes to demonstrate that these enzymes are required for normal cell-cycle progression and nuclear division under oxidative stress. This suggests that both enzymes play multiple roles in the maintenance of genome stability and tumor prevention. It is well known that 8-oxoG is a premutagenic lesion due to its capacity to mispair with adenine [18]. The action of the MUTYH enzyme on 8-oxoG:A mispairs can avoid mutation and, consequently, the development of tumor cells in humans. Additionally, studies using a docking approach suggested that the DNA repair activity of MUTYH is coupled with human proliferating cell nuclear antigen (hPCNA) and human replication protein A (hRPA) to replicate DNA [19–21]. The co-localization of MUTYH and the DNA mismatch repair enzymes MSH2/MSH6 with hPCNA at replication foci has been reported in previous studies [22,23].

The human *MUTYH* gene produces a variety of transcripts through alternative splicing (for a review, see reference [24]) and encodes multiple forms of the MUTYH protein, which are targeted to both the mitochondria and the nucleus [25]. Two germline mutations in the *MUTYH* gene that result in proteins containing the amino acid substitutions Y165C and G382D are related to MAP syndrome, an autosomal recessive disorder that results in a predisposition to multiple colorectal adenomas and carcinomas [26]. These mutations affect residues that are conserved in the MutY protein in *E. coli* (Tyr82 and Gly253). Tyrosine 82 is located in the pseudo-helix–hairpin–helix (HhH) motif and is predicted to function in mismatch specificity. Adenine glycosylase activity assays using Tyr82Cys and Gly253Asp mutant proteins with 8-oxoG:A and G:A substrates show that the activities of these enzymes are reduced significantly [26]. Goto et al. [27] have investigated fourteen MUTYH variants identified in patients with colorectal polyposis and/or with colorectal cancer and found that nine of those variants lead to impaired adenine DNA glycosylase activity. Moreover, another study has suggested the involvement of a bi-allelic germline mutation in *MUTYH* with an increased susceptibility to endometrial cancer [28]. However, studies concerning the germline MUTYH missense variants Y165C and G382D have not found any significant correlation between these mutants and an increased risk for prostate cancer [29]. Inherited variants in MUTYH are unlikely to contribute to the risk of lung carcinoma [30], despite the mounting evidence that oxidative damage is a key factor in tumorigenesis and the fact that the lung is a highly oxygenated organ. However, deficiency in both OGG1 and MUTYH proteins results in an increased incidence of cancer in the lung and small intestine [31].

Dorn et al. [32] demonstrated that the endogenous level of MUTYH protein depends on the expression level of the Mule E3 ligase. MUTYH is ubiquitinated *in vitro* and *in vivo* by the Mule E3 ligase between amino acids 475 and 535; this ubiquitination regulates both protein levels and subcellular localization. It was observed that sequence alterations in this region result in an increase in mutational frequency upon oxidative stress. This is due