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Review

Role of MUTYH in human cancer

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ABSTRACT

MUTYH, a human ortholog of MutY, is a post-replicative DNA glycosylase, highly conserved throughout evolution, involved in the correction of mismatches resulting from a faulty replication of the oxidized base 8-hydroxyguanine (8-oxodG). In particular removal of adenine from A:8-oxodG mispairs by MUTYH activity is followed by error-free base excision repair (BER) events, leading to the formation of C:8-oxodG base pairs. These are the substrate of another BER enzyme, the OGG1 DNA glycosylase, which then removes 8-oxodG from DNA. Thus the combined action of OGG1 and MUTYH prevents oxidative damage-induced mutations, *i.e.* GC- > TA transversions. Germline mutations in *MUTYH* are associated with a recessively heritable colorectal polyposis, now referred to as MUTYH-associated polyposis (MAP). Here we will review the phenotype(s) associated with MUTYH inactivation from bacteria to mammals, the structure of the MUTYH protein, the molecular mechanisms of its enzymatic activity and the functional characterization of *MUTYH* variants. The relevance of these results will be discussed to define the role of specific human mutations in colorectal cancer risk together with the possible role of MUTYH inactivation in sporadic cancer.

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1. Introduction

Reactive oxygen species (ROS) are important biological signalling molecules. Because they are also generated by exposure to exogenous chemicals and can damage macromolecules including DNA, intracellular ROS levels are carefully regulated. Conditions of oxidative stress, in which ROS levels become excessive, result in DNA damage. Redundant DNA repair pathways prevent the deleterious effects of this DNA oxidation. 8-hydroxyguanine (8-oxodG) – one of many oxidized DNA bases – has been extensively studied because of its miscoding properties. Frequent insertion of dAMP opposite 8-oxodG by replicative DNA polymerases causes T to G

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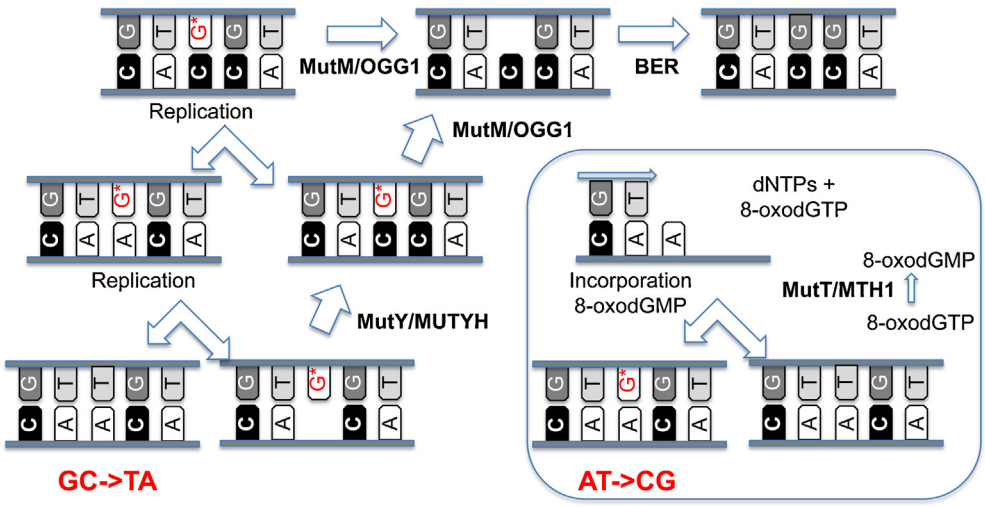

Bacterial name	Mammalian name	Enzymatic activity	Substrates[a]
MutM	OGG1, 8-oxoG DNA glycosylase 1	DNA glycosylase	8-oxoG and FaPyG opposite C in dsDNA
MutY	MUTYH, MutY homolog	DNA glycosylase	A opposite 8-oxoG, 2-OHA opposite G in dsDNA
MutT	MTH1, MutT homolog 1	hydrolase	8-oxodGTP, 2-OH-dATP 8-oxoGTP, 2-OH-ATP

Fig. 1. The three-tier system for removal of 8-oxodG.
Oxidative stress can introduce oxidized lesions in DNA. 8-oxodG can be removed by MutM/OGG1 and subsequent BER can restore the normal G:C base pairing. In the case of unrepaired 8-oxodG lesions, error-free translesion synthesis by replicative DNA polymerases leads to a C:8-oxodG pair, which is again a substrate for MutM. When A is misincorporated opposite the 8-oxodG as a consequence of inaccurate replication, its removal by MutY/MUTYH is followed by resynthesis using a much less error prone DNA polymerase. The long-patch BER results into a C/8-oxodG pair, again a substrate for MutM/OGG1.
Insert: Oxidative damage can also produce an oxidized dNTPs pool. MutT/MTH1 hydrolyzes 8-oxo-dGTP to 8-oxo-dGMP, effectively removing the triphosphate from the deoxynucleotide pool. In the absence of MutT/MTH1, 8-oxo-dGTP can be incorporated opposite template cytosines, resulting in a C:8-oxodG pair that could be corrected by MutM/OGG1. Replication might also be inaccurate because replicative polymerases can insert 8-oxo-dGTP opposite template A residues leading to A:8-oxodG mispairs. Accumulation of A:T > C:G transversions are characteristic of a *mutT* strain.
G*: 8-oxodG; BER: base excision repair. [a] these are DNA substrates for the mammalian enzymes; 2-OH-A: 2-hydroxyadenine.

transversion mutations [1]. In *E. coli*, these mutations are prevented by the combined action of the base excision repair (BER) DNA glycosylases MutM and MutY which remove 8-oxodG from 8-oxodG:C and adenine from 8-oxodG:A mispairs, respectively [2,3]. Following MutY-mediated removal of A from 8-oxodG:A, BER-mediated resynthesis generates C:8-oxodG base pairs which are restored to C:G by BER initiated by MutM. The MutT hydrolase, which degrades 8-oxodGTP in the dNTP pool to the monophosphate to prevent incorporation of promutagenic 8-oxodGMP into DNA, provides a third level of protection against the effects of excess ROS [4]. Inactivation of any of these genes confers a mutator phenotype and *mutM*, *mutY*, and *mutT* single mutants are weak, moderate, and strong mutators, respectively [5]. This three-tier error avoidance repair system is referred to as the GO pathway [6] (Fig. 1) and is generally conserved in animals and plants [7]. Mismatch repair (MMR), the major pathway for the correction of replication errors, can also remove mismatches containing oxidized bases [8–10]. The pronounced mutator phenotype associated with inactivation of MMR genes in bacteria (*mutSHL*) as well as in mammalian cells (*MSH2*, *MSH6*, *MLH1* and *PMS2*) is mostly due to incorrect nucleotide selection or strand slippage, but can be modulated to some extent by the level of oxidative damage [11].

While no human disease has been definitely associated with defective OGG1 or MTH1 (the mammalian MutM and MutT homologs) activities, mutations in *MUTYH* (the gene encoding the human MutY homolog) or in MMR genes are respectively implicated in MUTYH-Associated Polyposis (MAP) [12–14] and Hereditary Non-Polyposis Colorectal Cancer (HNPCC or Lynch syndrome). Lynch syndrome is the genetic disease caused by a germline mutation in a MMR gene and the defective MMR activity results in microsatellite instability (MSI) in the DNA of neoplastic cells [for a recent review see ref. [15]]. MAP is a recessively heritable colorectal polyposis linked to an increased risk of colorectal cancer (CRC) and tumors occurring in MAP patients bear distinctive somatic G:C to T:A transversions in the tumor suppressor *APC* gene. Thus inactivation of two repair pathways acting at replication to remove mismatches is associated with syndromes of increased CRC susceptibility.

Here we review the phenotypic characteristics associated with MUTYH inactivation in different organisms and discuss their possible impact on the clinical phenotype. For other recent reviews on oxidative damage repair refers to [16–18].

2. Mutator phenotype associated with loss of mutY

2.1. Bacteria

The DNA 8-oxodG repair enzymes are present in all large phylogenetic groups, with MutM homologues being the most widely conserved. In contrast, MutY homologues are absent from insects, annellids and some fungi, including *Saccharomyces cerevisiae* [7]. *MutY* strains of several microorganisms share with *E. coli* the increased frequency of G:C to T:A transversions, while the extent of the mutator phenotype associated with loss of MutY function

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