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MINIREVIEW

The GO System Protects Organisms from the Mutagenic Effect of the Spontaneous Lesion 8-Hydroxyguanine (7,8-Dihydro-8-Oxoguanine)

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INTRODUCTION

The GO system is an error avoidance pathway devoted to enhancing the fidelity of DNA replication (31, 35). Although the system has been most fully characterized for *Escherichia coli*, evidence already exists for similar repair proteins in other prokaryotes (23, 27) and in higher eukaryotes (29, 52). The GO system in *E. coli* is composed of at least three proteins, MutM, MutT, and MutY. These three proteins are responsible for removing an oxidatively damaged form of guanine from DNA and the nucleotide pool and for the correction of error-prone translesion synthesis. The damaged form of guanine is 7,8-dihydro-8-oxoguanine (also known as 8-hydroxyguanine or a GO lesion [Fig. 1A]).

Despite the fact that the GO system appears to be devoted to the prevention of errors emanating solely from the GO lesion, it is one of the more important fidelity-enhancing systems characterized to date, as judged by the mutation rates of strains lacking common error avoidance mechanisms (31). A knockout of the GO system results in mutation rates that are of the same order of magnitude as those in mutants lacking the polymerase III proofreading subunit (*mutD*) and about an order of magnitude higher than those in mutants lacking the methyl-directed mismatch repair system (*dam*, *mutHLS*) (31, 32).

The high mutation rate observed in a GO system knockout is attributable in large part to the abundance and miscoding potential of the GO lesion. The GO lesion is one of the most stable products of oxidative damage to DNA (17). Ionizing radiation and other treatments that generate active oxygen species produce GO lesions (17). However, such treatments are not required in order to generate GO lesions in the cell. Mutator strains grown aerobically or anaerobically have equal mutation rates (32), suggesting that endogenous processes, such as electron transport or lipid peroxidation, can produce the active oxygen species that lead to GO lesions. Steady-state levels of this adduct have been estimated to be 10^4 per cell in humans and 10^5 per cell in rodents (20). In addition to its high abundance, the GO lesion has miscoding potential. The miscoding potential of the lesion might seem surprising given the adduct's benign appearance—a nondistorting lesion that is situated outside the base-pairing region (40). However, it forms a stable base pair with A, where A is *anti* and the GO lesion is *syn* (24). Rotation of the GO lesion to the *syn* conformation is favored because it relieves steric interactions between the C-8 keto group and the sugar ring (40).

Oxidative stress has been implicated as an important causative agent of mutagenesis, carcinogenesis, aging, and a number of diseases (for reviews see references 19 and 41). In this minireview we present recent developments that characterize the roles of the MutM, MutT, and MutY proteins in the GO system, which is responsible for handling one specific form of oxidative damage. For reviews of other DNA repair systems devoted to oxidative damage, see references 18, 19, 22, and 41.

MutM

MutM removes GO lesions from chromosomal DNA. The *mutM* gene is a mutator that specifically increases the rate of G · C → T · A transversions when the gene is disrupted (11). It maps to 81 min on the *E. coli* chromosome (11). Cloning and sequencing of the *mutM* gene revealed that it was identical to the *fpg* gene from *E. coli* (33).

The FPG protein was originally characterized as a glycosylase active on formamidopyrimidine adducts that result from the opening of the imidazole ring of guanine (13). Subsequent work has shown that the glycosylase is active on a variety of modified ring-opened purines (9, 12, 14) and that the enzyme also has apurinic/apyrimidinic (AP) endonuclease (6, 39) and 5′-terminal deoxyribose phosphatase (21) activities. The AP endonuclease reaction proceeds via a β-elimination reaction, resulting in a gap limited at the 3′ and 5′ ends by phosphoryl groups (6, 39). Other enzymes subsequently excise the resulting 3′ end and repair the gap.

The elevated rate of G · C → T · A transversions in a *mutM* strain cannot be attributed to the loss of an enzyme that removes ring-opened purines. While these adducts are known to block DNA replication and could lead to cell death (10), they are not specific for induction of G · C → T · A transversions. Therefore, it was suspected that MutM might also act on a different substrate that could be mutagenic.

A protein called 8-oxoguanine DNA glycosylase was isolated from *E. coli* on the basis of its ability to remove GO lesions from DNA (46). This enzyme turned out to be identical to MutM (FPG protein). In vivo DNA replication studies using templates modified with GO lesions have

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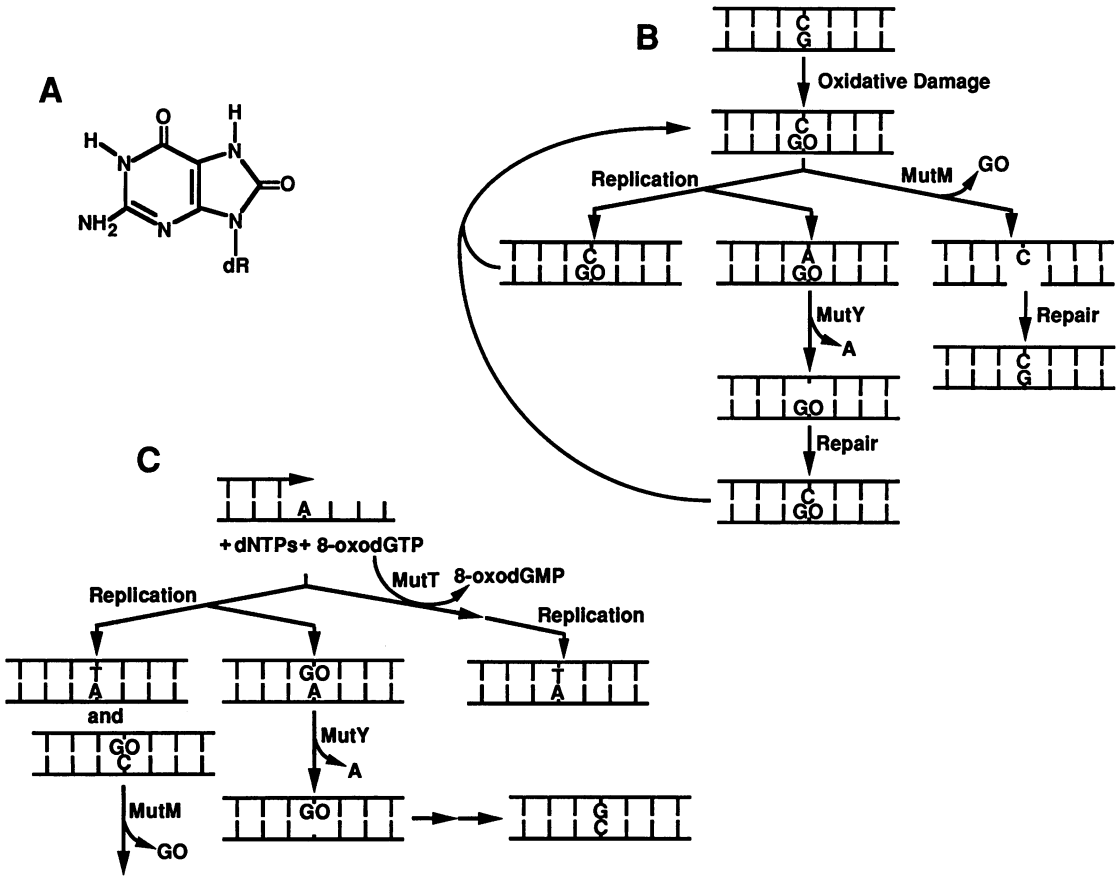

FIG. 1. The GO system. (A) 7,8-Dihydro-8-oxoguanine (8-hydroxyguanine). This is the structure of the predominant tautomeric form of the GO lesion. (B) Oxidative damage can lead to GO lesions in DNA. The GO lesions can be removed by MutM protein, and subsequent repair can restore the original G · C base pair. If the GO lesion is not removed before replication, translesion synthesis can be accurate, leading to a C/GO pair, which is a substrate for MutM protein. However, translesion synthesis by replicative DNA polymerases is frequently inaccurate, leading to the misincorporation of A opposite the GO lesion. MutY removes the misincorporated adenine from the A/GO mispairs that result from error-prone replication past the GO lesion. Repair polymerases are much less error prone during translesion synthesis and can lead to a C/GO pair—a substrate for MutM. (C) Oxidative damage can also lead to 8-oxo-dGTP. MutT is active on 8-oxo-dGTP and hydrolyzes it to 8-oxo-dGMP, effectively removing the triphosphate from the deoxynucleotide pool. If MutT were not active and replication occurred with 8-oxo-dGTP in the deoxynucleotide pool, replication would be largely accurate because the polymerase preferentially inserts the correct T opposite A residues. However, inaccurate replication could result in the misincorporation of 8-oxo-dGTP opposite template A residues, leading to A/GO mispairs. MutY could be involved in the mutation process because it is active on the A/GO substrate and would remove the template A, leading to the A · T→C · G transversions that are characteristic of a *mutT* strain. The 8-oxo-dGTP could also be incorporated opposite template cytosines, resulting in a damaged C/GO pair that could be corrected by MutM.

shown that polymerases can specifically misincorporate an A opposite the GO adduct (37, 50). In these studies, transformation of *E. coli* with either single-stranded phage DNA or double-stranded plasmid DNA, each containing site-specific GO lesions, resulted in a specific G · C → T · A transversion at the site of the adduct. A site-specific GO lesion in a single-stranded shuttle vector transformed into mammalian cells gave the same results (36). Further, in vitro replication studies using eukaryotic polymerase α, β, or δ or *E. coli* polymerase I (Klenow fragment) showed that all the polymerases tested could specifically misincorporate an A opposite the GO adduct (44). Interestingly, replicative DNA polymerases were much more error prone than the repair polymerases tested (44). The specificity of misincorporation of A opposite GO adducts could account for the specific increase in G · C → T · A transversions in a *mutM* strain. Thus, MutM can remove both the cell-killing ring-opened purine lesions and the mutagenic GO adducts. Both ring-opened purines and GO lesions can be generated by oxidative damage to DNA (9).

MutY

MutY corrects error-prone DNA synthesis past GO lesions. Like a knockout of *mutM*, a knockout of the *mutY* gene leads to a specific increase in G · C → T · A transversions (38). The *mutY* gene maps to 64 min on the *E. coli* chromosome (38). By use of an in vivo recombination system (30), the *mutY* gene was cloned and sequenced (34). It encodes a 350-amino-acid protein with a mass of 39 kDa. A gene called *micA* with the same phenotype as *mutY* was subsequently identified (42). Sequencing of the *micA* clone proved that the two genes were identical (48).

Work on the correction of mismatches in heteroduplex DNA hinted at a potential role for MutY in A/G mispair correction (25, 45). These studies showed that A/G mispairs

could be corrected to C · G base pairs by a mechanism independent of DNA methylation and the mismatch repair system. Subsequent studies showed that MutY was responsible for the A/G mispair correction (3). While initial experiments using partially purified extracts suggested that MutY removes a small tract of DNA containing the mispaired A residue (26), subsequent purification of the enzyme showed that MutY is a glycosylase that removes the mispaired A from an A/G mismatch in heteroduplex DNA (4) and that the enzyme may also have an associated AP endonuclease activity (49).

Because *mutM* and *mutY* strains specifically stimulate G · C → T · A transversions, the genes were suspected to be involved in a common repair pathway. MutY is active on an A/GO mispair, a substrate that mimics the product of error-prone synthesis past a GO lesion (31). MutY removes the undamaged A from this damaged mispair. Protection assays and gel shift analysis showed that MutY remains bound to the DNA after removal of the A (35). This positioning not only protects the GO adduct from attack by the MutM protein, preventing the loss of one base of information and a double strand break, but may also serve as a signal to other repair proteins that can complete the repair process (35).

In addition to the biochemical evidence mentioned above, there is strong genetic evidence linking *mutM* with *mutY* in the GO system. They have nearly identical mutation spectra in the *lacI* forward mutation system, and both stimulate specifically G · C → T · A transversions (11, 38). Further, overexpression of MutM from a plasmid can completely complement a *mutY* strain (31). Similarly, a chromosomal suppressor of *mutY*, called Sup17, has been isolated. Sup17 overproduces the MutM protein by about 15-fold (31). Because overexpression of the MutM protein would have no effect on the repair of undamaged A/G mispairs, these complementation results strongly suggest that although MutY is active on both the A/G and A/GO mispair substrates in vitro, the major substrate in vivo must be the A/GO mispair. Finally, the *mutM mutY* double mutant has a G · C → T · A transversion rate that is 20-fold higher than the sum of the mutation rates of the mutators alone (31). This dramatic increase in mutation rate can best be explained by the model shown in Fig. 1B, in which MutM and MutY prevent mutations by chromosomal GO lesions in an interdependent manner. If both of the proteins are inactivated, the cell's defenses against the mutagenic lesion in DNA are largely compromised.

MutT

MutT removes oxidatively damaged dGTP from the nucleotide pool. The *mutT* mutator gene (47) maps to about 2.5 min on the *E. coli* chromosome (5). Inactivation of the gene leads to a specific increase in A · T → C · G transversions (51). Experiments with bacteriophage λ indicate that DNA replication is required for expression of the *mutT* phenotype (15). In vitro replication studies with M13 DNA show that the A · T → C · G transversions in a *mutT* strain are mediated by A/G, rather that C/T, mispairs (43).

The *mutT* gene encodes a 129-amino-acid protein with a mass of 15 kDa (1). The MutT protein has a weak dGTPase activity (8), and it was proposed that MutT might be active on a particular conformation of dGTP, possibly the *syn* conformation (2, 7). This hypothesis would require that MutT function directly with the replication machinery, for its reaction rate is much slower than *syn-anti* rotation and therefore its presence would not significantly alter the dGTP *syn*/dGTP*anti* ratio in the cytosol. However, labeled MutT protein shows no interaction or association with other *E. coli* proteins, including those known to be involved in DNA replication (8).

Recently, 7,8-dihydro-8-oxo-dGTP (8-oxo-dGTP) has been identified as a substrate for MutT (28). MutT is three orders of magnitude more active on 8-oxo-dGTP than on dGTP (28). It degrades 8-oxo-dGTP to 8-oxo-dGMP, thus eliminating 8-oxo-GTP as a substrate for DNA synthesis. The 8-oxo-dGTP nucleotide is a potent mutagenic substrate for DNA replication. *E. coli* DNA polymerase α inserts 8-oxo-dGTP with equal efficiency opposite C or A in template DNA and with about 3 to 4% efficiency relative to the natural substrates (dGTP and dTTP, respectively) (28).

The evidence suggests that 8-oxo-dGTP is the biologically relevant substrate leading to the mutator phenotype of a *mutT* strain. Misincorporation of 8-oxo-dGTP specifically occurring opposite template adenines would lead to A/GO mispairs. Subsequent replication would result in an A · T → C · G transversion—the characteristic phenotype of a *mutT* strain. The model agrees with the finding that A · T → C · G transversions in a *mutT* strain involve some form of an A/G, rather than a C/T, mispair (43). The model also confirms other established data regarding *mutT*: replication is required for observation of the *mutT* phenotype (15); MutT does not associate with other proteins, including the replication complex (8); and MutT is not involved in postreplication repair or recombination (16).

CONCLUSION

The error avoidance pathway that has evolved to prevent the GO lesion from causing mutations in the *E. coli* chromosome is elaborate (Fig. 1). The cell faces two distinctly different problems relating to GO adducts. One problem is the miscoding potential of GO lesions in chromosomal DNA. The other problem is the potential for misincorporation of 8-oxo-dGTP into DNA. Mutation rates are minimized by having multiple lines of defense to protect the cell from the deleterious effects of GO lesions.

In the case of chromosomal GO lesions, the cell relies on MutM and MutY to prevent G · C → T · A transversions (31, 35). MutM removes GO lesions from chromosomal DNA (46). If MutM fails to remove all of the GO adducts before DNA replication, translesion synthesis can be inaccurate, leading to the misincorporation of A opposite the GO adduct (44). In vitro studies using purified MutM have shown that while MutM is less active on the A/GO substrate than on C · GO, it can remove the GO lesion from either heteroduplex (35, 46). Removal of the GO from the A/GO mispair by MutM would lead to a G · C → T · A transversion. However, if MutY is present in the reaction mixture, it has a higher affinity for the A/GO mispair and removes the misincorporated A (35). MutY remains bound to the site after the reaction, preventing MutM from attacking the GO lesion opposite the AP site (35). If MutM were to act on the AP/GO site, it would lead to the loss of one base of information and a double strand break. The bound MutY may also serve as a signal to other proteins that can advance the DNA repair process (35).

The other problem that confronts the cell is the misincorporation of 8-oxo-dGTP into DNA. Again, the cell relies on two systems to prevent errors due to this mutagenic substrate. First, MutT protein hydrolyzes 8-oxo-dGTP to 8-oxo-dGMP (28). This virtually eliminates the triphosphate from the nucleotide pool and helps to prevent its misincorporation

opposite template adenines. The second defense occurs during the DNA polymerization step, in which nucleotide selection and/or editing by the DNA polymerase provides a bias of at least two orders of magnitude against the incorporation of 8-oxo-dGTP, rather than dTTP, opposite template adenines in DNA (28).

The GO system that has been characterized for *E. coli* demonstrates that the cell goes to great lengths to prevent mutations due to GO adducts in DNA or the nucleotide pool. Its defense begins with the enzymatic and nonenzymatic systems that work to prevent active oxygen species from damaging DNA. Active oxygen species that escape the primary defenses can damage nucleic acids (19, 41). A second line of defense acts to eliminate this damage. MutM and MutT are typical of this second line of defense. The MutY protein and DNA polymerases provide yet another level of defense against the mutagenic potential of the GO adduct in DNA or the nucleotide pool.

The GO system is critical to the maintenance of replication fidelity. A *mutM mutY* double mutant has a mutation rate that is of the same order of magnitude as the mutation rate observed when the polymerase III proofreading function is disabled, and it is significantly higher than the mutation rate of a strain lacking the methyl-directed mismatch repair system (31). The mutation rate of a strain lacking the GO system provides convincing evidence that active oxygen species pose a significant threat to the cell.

The GO lesion is ubiquitous in nature and represents one of the most stable products of oxidative damage to DNA (17, 19). While replication past a GO adduct has been tested for only a limited number of polymerases, all those tested misincorporate A opposite GO lesions in DNA to some extent (36, 37, 44, 50). These include both eukaryotic and prokaryotic polymerases. Evidence for repair proteins in higher eukaryotes similar to the ones characterized for *E. coli* is already beginning to emerge. Proteins with activities similar to those of MutM (29) and MutY (52) have been reported to exist in mammalian cells. Thus, the GO system may play a crucial role in maintaining replication fidelity in a wide range of organisms.

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