

Bacterial DNA repair genes and their eukaryotic homologues: 2. Role of bacterial mutator gene homologues in human disease. Overview of nucleotide pool sanitization and mismatch repair systems*

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Since the discovery of the first *E. coli* mutator gene, *mutT*, most of the mutations inducing elevated spontaneous mutation rates could be clearly attributed to defects in DNA repair. MutT turned out to be a pyrophosphohydrolase hydrolyzing 8-oxodGTP, thus preventing its incorporation into DNA and suppressing the occurrence of spontaneous AT→CG transversions. Most of the bacterial mutator genes appeared to be evolutionarily conserved, and scientists were continuously searching for contribution of DNA repair deficiency in human diseases, especially carcinogenesis. Yet a human MutT homologue – hMTH1 protein – was found to be overexpressed rather than inactivated in many human diseases, including cancer. The interest in DNA repair contribution to human diseases exploded with the observation that germline mutations in mismatch repair (MMR) genes predispose to hereditary non-polyposis colorectal cancer (HNPCC). Despite our continuously growing knowledge about DNA repair we still do not fully understand how the mutator phenotype contributes to specific forms of human diseases.

Keywords: DNA damage, DNA repair, MutT protein, human MutT homologue, mismatch repair, hereditary non-polyposis colorectal cancer

INTRODUCTION

Maintaining low mutation rates is essential for the cell stability. However, natural isolates of *Escherichia coli* have been found to have elevated mutation rates (Matic *et al.*, 1997) and strains showing this phenotype are termed mutators. Although the mutator phenotype may have some beneficial effects allowing better adaptation to environmental

conditions, it also generates many deleterious and lethal mutations (Funchain *et al.*, 2000).

The first described *E. coli* mutator gene – *mutT1* (Treffers *et al.*, 1954) which specifically increases, from 100 to 10000-fold, the occurrence of AT→CG transversions (Yanofsky *et al.*, 1966) was shown to encode MutT pyrophosphohydrolase specifically acting on 8-oxodGTP (Maki & Sekiguchi, 1992), thus preventing incorporation of this po-

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Abbreviations: (h)MTH1–2, (human) MutT homologue 1–2; 2-oxoA, 8-oxoA and 8-oxoG, 2-oxoadenine, 8-oxoadenine and 8-oxoguanine, respectively, also refers to these oxidized bases in (deoxy)nucleosides and (deoxy)nucleotides; HNPCC, hereditary non-polyposis colorectal cancer; IDL, insertion/deletion loop; MLH1–3, mutL homologue 1–3; MMR, mismatch repair; MSH1–MSH6, MutS homologues 1–6; MSI, microsatellite instability; MutL α , MLH1-PMS2 heterodimer; MutS α , MSH2-MSH6 heterodimer; MutS β , MSH2-MSH3 heterodimer; MYH, MutY homologue; NDPK, nucleoside diphosphate kinase; NER, nucleotide excision repair; NSCLC, non-small cell lung cancer; OGG1-2, 8-oxoguanine DNA glycosylase 1-2; PMS1-2, post meiotic segregation protein 1-2; RFC, replication factor C; RPA, replication protein A; SSB, single-stranded DNA binding protein.

tentially mutagenic substrate into DNA. The list of *E. coli* mutators was extended further by other DNA repair gene products, such as the base excision repair (BER) glycosylases MutM/Fpg and MutY (for details see Krwawicz *et al.*, this issue), mismatch repair (MMR) proteins MutH, MutS and MutL (for details see below), and MutU/UvrD — helicase II engaged in MMR, nucleotide excision repair (NER) (Truglio *et al.*, 2006; for details see Maddukuri *et al.*, this issue), and recombination repair (RR) (for details see Vidakovic *et al.*, 2005; O'Driscoll & Jeggo, 2006; Nowosielska, this issue). Additionally, Miller (1996) extended the list of *E. coli* mutators by *ung*, *sodA*, *dam*, *oxyR*, and *polA* strains defective in uracil-DNA glycosylase, superoxide dismutase, DNA adenine methyltransferase, positive regulator of oxidative damage response, and DNA polymerase I, respectively, but all of them are rather weak mutators and thus are not considered as major *E. coli* mutators. The list of *E. coli* mutators is not limited to strains defective in DNA repair, but also includes strains encoding mutated tRNAs, such as *mutA* and *mutC* (Slupska *et al.*, 1996), and mutated 3'→5' proofreading ϵ subunit of the DNA polymerase III holoenzyme — *mutD/dnaQ* (Echols *et al.*, 1983), but they are not subject of this review.

Counterparts of bacterial DNA repair proteins have been found in eukaryotic organisms, including humans. Moreover, it has been shown that DNA repair deficiency results in accumulation of DNA damage, which may contribute to aging and development of human diseases, including cancer and neurological diseases (Brooks, 2002; Krokan *et al.*, 2004; Olinski *et al.*, 2007). The present review describes two DNA repair and damage prevention systems — nucleotide pool sanitization and mismatch repair. For an overview of the human repair proteins described below see Table 1.

NUCLEOTIDE POOL DAMAGE AS SOURCE OF MUTATIONS AND ITS PREVENTION BY *E. COLI* MutT PROTEIN

Various DNA damaging agents react with nucleic acid bases present not only in DNA (for a review see Krwawicz *et al.*, this issue), but also in precursors for DNA synthesis, i.e. 2'-deoxyribonucleoside-5'-triphosphates (dNTPs). Generally, bases in dNTPs are more easily accessible to damage than bases in DNA, where they are involved in secondary and tertiary DNA as well as chromosomal structures (Topal & Baker, 1982; Kamiya & Kasai, 1995). Modified dNTPs may induce mutations, since they are incorporated into DNA by DNA polymerases with an efficiency within the range of 10^{-5} – 10^{-2} of unmodified dNTPs incorporation (for examples see: Snow *et*

al., 1984; Purmal *et al.*, 1994; Miller *et al.*, 2000; Imoto *et al.*, 2006). In fact, one of the most common oxidative modifications in the dNTP pool — 8-oxodGTP — has been shown to be incorporated almost 24 times more efficiently opposite template A than opposite template C by human polymerase β (Miller *et al.*, 2000). Thus, 8-oxodGTP misincorporated opposite A may lead to AT→CG transversions (for details see Fig. 1) both *in vitro* (Pavlov *et al.*, 1994; Minnick *et al.*, 1994) and *in vivo* (Inoue *et al.*, 1998; Satou *et al.*, 2005).

To prevent 8-oxodGTP incorporation to DNA, *E. coli* cells are equipped with the MutT protein, which was discovered as a nucleoside triphosphate pyrophosphohydrolase dephosphorylating all canonical ribo- and 2'-deoxyribonucleoside-5'-triphosphates to their corresponding 5'-monophosphates and inorganic pyrophosphate ($\text{dNTP} + \text{H}_2\text{O} \rightarrow \text{dNMP} + \text{PPi}$) (Bhatnagar & Bessman, 1988; Bhatnagar *et al.*, 1991). Initially, the MutT protein was proposed to prevent the occurrence of AT→CG transversions by degrading a specific form of dGTP, or dGTP in the *syn* conformation, which can mispair with A during replication (Akiyama *et al.*, 1989; Bhatnagar *et al.*, 1991). However, the discovery that the MutT protein is over 2000 times more active towards 8-oxodGTP than towards dGTP, has pointed out to its true role (Maki & Sekiguchi, 1992). Recently it appeared that the MutT protein is also able to efficiently hydrolyze 8-oxodGDP (Ito *et al.*, 2005). 8-OxodGTP and 8-oxodGDP are interconvertible, probably by the actions of nucleoside diphosphate kinase (NDPK) and nucleoside triphosphatase (Hayakawa *et al.*, 1995; Kamiya & Kasai, 1999). Furthermore, MutT protein also prevents transcriptional errors by dephosphorylation of ribonucleotides 8-oxoGDP and 8-oxoGTP, which otherwise can be incorporated into RNA opposite A present in the DNA template (Taddei *et al.*, 1997; Ito *et al.*, 2005).

A comparison of the amino-acid sequence of the MutT protein with sequences present in databases has revealed similarities with putative products of uncharacterized open reading frames (Orfs) from bacteria to mammals, and also with viral gene products of unknown function. All these similarities were concentrated in the same MutT segment consisting of about 30 amino acids, with six positions containing strictly conserved amino-acid residues. Based on this sequence homology the MutT protein family was distinguished as a family of proteins containing the MutT signature sequence, i.e. $\text{Gx}_5\text{Ex}_7\text{REUxEEx}_2\text{U}$ (where x means any residue and U means a bulky aliphatic or hydrophobic residue, i.e. I, L, V, M, F, Y or W) (Koonin, 1993). In consequence, functional MutT homologues from *Proteus vulgaris* and *Streptococcus pneumoniae* were identified, characterized, and shown to complement the mutator phenotype of the

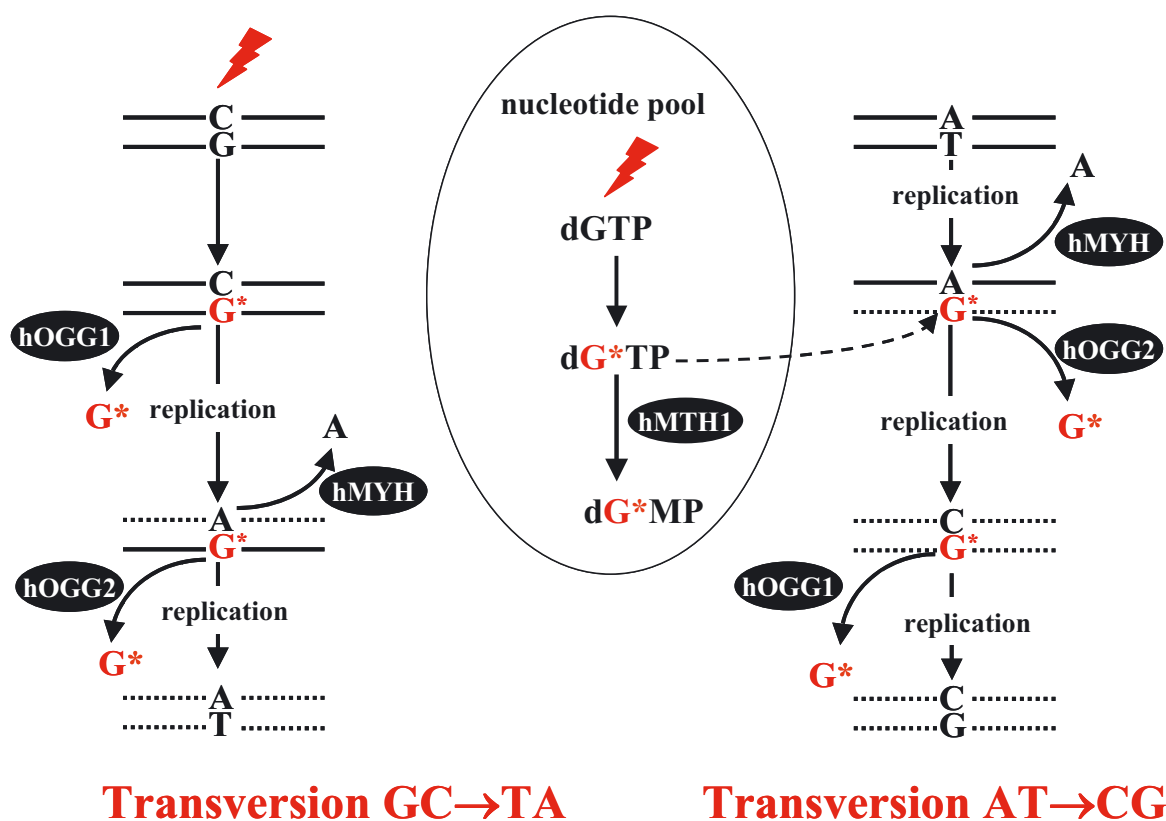


Figure 1. Prevention of transversion mutations by mammalian GO system (adapted from scheme proposed for *E. coli* by Michaels and Miller, 1992).

8-OxoG is formed in DNA both by direct guanine oxidation and by 8-oxodGTP incorporation from nucleotide pool. 8-OxodGTP is incorporated mainly opposite A, and thus, if unrepaired may lead to AT→CG transversion. When 8-oxoG is present in DNA it may pair with A upon replication, which leads to GC→TA transversions. hMTH1 pyrophosphohydrolase, and hOGG1, hOGG2 and hMYH glycosylases act together to prevent these mutations. *E. coli* cells lack hOGG2 protein, 8-oxodGTP is hydrolyzed by MutT protein, 8-oxoG is excised from pair with C by MutM glycosylase, and A is excised from pair with 8-oxoG by MutY glycosylase. G*, 8-oxoG.

mutT E. coli strain (Kamath & Yanofsky, 1993; Bulions *et al.*, 1994; Mejean *et al.*, 1994). Furthermore, human, rat and mouse MutT homologue-1 (MTH1) genes have been identified, cloned and shown to suppress the increased occurrence of AT→CG transversions in *E. coli mutT* cells (Mo *et al.*, 1992; Sakumi *et al.*, 1993; Furuichi *et al.*, 1994; Cai *et al.*, 1995; Kakuma *et al.*, 1995). Despite the functional homology, human MTH1 and *E. coli* MutT share only 30 residues (23%), 14 of which are contained in the conserved 23-residue module, while the other 16 residues are scattered throughout the whole molecules (Shimokawa *et al.*, 2000).

The MutT protein family appeared to contain also proteins active in many other reactions, distinct from the MutT-like activity, including hydrolysis of nucleoside-5'-di- and triphosphates, dinucleoside and diphosphoinositol polyphosphates, nucleotide sugars and alcohols, dinucleotide coenzymes and RNA caps (Bessman *et al.*, 1996; McLennan, 2006). In all the cases where the enzymatic function was known these

proteins appeared to be pyrophosphohydrolases that acted upon a nucleoside diphosphate linked to some other moiety, X, hence the name "Nudix" hydrolases was proposed for this family, with the term "MutT signature sequence" changed to "Nudix box". MutT and its functional homologues constitute a subfamily of Nudix hydrolases, where X = phosphate group. It has been proposed that Nudix hydrolases are "housecleaning" enzymes which control the level of cellular metabolism by-products, metabolic intermediates and signaling compounds, whereas the specific role of MutT proteins is to "sanitize" the dNTP pool (Bessman *et al.*, 1996).

The importance of nucleotide pool sanitization is further highlighted by the observation that dUT-Pase, enzyme responsible for elimination of another damaged dNTP, dUTP, is essential for survival of *E. coli* (el-Hajj *et al.*, 1988), *S. cerevisiae* (Gadsden *et al.*, 1993; Guillet *et al.*, 2006) and *C. elegans* (Dengg *et al.*, 2006). Interestingly, it was shown recently that abrogation of the S-phase checkpoint gene *clk-2* rescued

Table 1. Overview of bacterial MutT and MMR proteins and their eukaryotic counterparts

<i>E. coli</i> protein	Function	<i>S. cerevisiae</i> homologue	Human homologue	Function	Gene (other aliases)	Protein	Size (kDa)	Chromosome location	Gene ID at NCBI site
MutT	8-oxodGTPase; active also on 2-oxodATP, 8-oxodATP, 8-Cl-dGTP, 8-oxoGTP, 2-oxoATP; inhibited by 8-oxodGDP and 2-oxodADP	Pcd1p (YLR151c); 8-oxodGTPase; primarily identified as CoA hydro-lase	MTH1 (NUDT1)	8-oxodGTPase; active also on 2-oxodATP, 8-oxodATP, 8-Cl-dGTP, 8-oxoGTP, 2-oxoATP; inhibited by 8-oxodGDP and 2-oxodADP	MTH1 (NUDT1)	hMTH1	18 19.5 20.3	7p22	4521
	8-oxodGTP and 8-oxoGDP	MTH2 (NUDT15)	MTH2 (NUDT15); FLJ10956; MGC104352; RP11-90M2.1	8-oxodGTPase?	MTH2	MTH2	18.6	13q14.2	55270
MutS	binds mismatches and small IDLs	MutSα (Msh2-Msh6)	MutSα (MSH2-MSH6)	8-oxodGTPase; primarily identified as ADP-sugar pyrophosphatase	NUDT5 (YSA1H; hYSAH1)	NUDT5	24.3	10p14-p13	11164
		MutSβ (Msh2-Msh3)	MutSβ (MSH2-MSH3)	binds mismatches and small IDLs	MSH2 (COCA1; FCC1; HNPCC; HNPCC1)	MSH2	104.7	2p22-p21	4436
		MutSγ (Msh4-Msh5)	MutSγ (MSH4-MSH5)	binds IDLs	MSH6 (GTBP; HNPCC5; HSAP)	MSH6	152.8	2p16	2956
		MutSδ (Msh4-Msh5)	MutSδ (MSH4-MSH5)	meiotic recombination	MSH3 (DUP; MGC163306; MGC163308; MRP1)	MSH3	127.4	5q11-q12	4437
MutL	molecular matchmaker; activates MutH endonucleolytic activity in MutS-, ATP- and mismatch-dependent manner	MutLα (Mlh1-Pms1)	MutLα (MLH1-PMS2)	possible role in MR since PMS1 knockout mice exhibit MSI	MSH4 (RP11-262K24.2)	MSH4	104.8	1p31	4438
		MutLβ (Mlh1-Mlh2)	MutLβ (MLH1-PMS1)	involved in repair of base-base mismatches and single-nucleotide IDLs; participates in meiosis	MSH5 (XXbac-BCX40G17.5; DKFZ-p434C1615; G7; MGC2939; MutSH5; NG23)	MSH5	94.7 93.0 92.9	6p21.3	4439
MutH	endonuclease; incises the unmethylated strand at hemimethylated GATC sites	MutHγ (Mlh1-Mlh3)	MutHγ (MLH1-MLH3)	involved in repair of base-base mismatches and single-nucleotide IDLs; participates in meiosis	MLH1 (COCA2; FCC2; HNPCC; HNPCC2; MGC5172; hMLH1)	MLH1	84.6	3p21.3	4292
		MutHδ (Mlh1-Mlh3)	MutHδ (MLH1-MLH3)	involved in repair of base-base mismatches and single-nucleotide IDLs; participates in meiosis	PMS2 (HNPCC4; PMS2CL; PMSL2)	PMS2	95.8	7p22.2	5395
MutI	molecular matchmaker; activates MutH endonucleolytic activity in MutS-, ATP- and mismatch-dependent manner	MutIα (Mlh1-Pms1)	MutIα (MLH1-PMS2)	possible role in MR since PMS1 knockout mice exhibit MSI	PMS1 (DKFZp781M0253; HNPCC3; PMSL1; hPMS1)	PMS1	105.8	2q31.1	5378
		MutIβ (Mlh1-Mlh2)	MutIβ (MLH1-PMS1)	involved in repair of base-base mismatches and single-nucleotide IDLs; participates in meiosis	MLH3 (HNPCC7; MGC138372)	MLH3	163.7	14q24.3	27030
MutJ	endonuclease; incises the unmethylated strand at hemimethylated GATC sites	MutJγ (Mlh1-Mlh3)	MutJγ (MLH1-MLH3)	involved in repair of base-base mismatches and single-nucleotide IDLs; participates in meiosis	none	none	none	none	none
		MutJδ (Mlh1-Mlh3)	MutJδ (MLH1-MLH3)	involved in repair of base-base mismatches and single-nucleotide IDLs; participates in meiosis	none	none	none	none	none

UvrD (helicase II)	unwinds DNA from a nick created by MutH toward mismatch site to allow ssDNA excision	none			
SSB	stabilizes single-stranded gap; facilitates excision and DNA resynthesis	RPA (RF-A; HSSB) (RPA1/RPA2/RPA3 and RPA1/RPA3/RPA4 heterotrimeric complexes)	RPA1 (HSSB; REPA1; RF-A; RP-A; RPA70)	RPA1	17p13.3 6117
		Rfa (Rpa) (Rfa1p/Rfa2p/Rfa3p heterotrimeric complex)	RPA2 (REPA2)	RPA2	1p35 6118
			RPA3 (REPA3; RPA14)	RPA3	7p22 6119
			RPA4 (RPA1-117P19.1, HSU24186, MGC120333, MGC120334)	RPA4 (RPA2 homologue)	Xq21.33 29935
RecJ	5'→3' exonuclease	5'→3' exonuclease; interacts with MSH2, MSH3 and MutL α	EXO1 (HEX1, hExo1)	EXO1	1q42-q43 9156
ExoVII	5'→3' and 3'→5' exonuclease				
ExoI	3'→5' exonuclease	none			
ExoX					
γ - δ complex	β -clamp loader	Rfc complex (consists of five subunits: Rfc1p, Rfc2p, Rfc3p, Rfc4p and Rfc5p)	RFC1 (A1, MGC51786, MHCBFB, PO-GA, RECC1, RFC, RFC140)	RFC1	4p14-p13 5981
			RFC2 (A1, MGC3665, RFC40)	RFC2	7q11.23 5982
			RFC3 (MGC5276, RFC38)	RFC3	13q12.3-q13 5983
			RFC4 (A1, MGC27291, RFC37)	RFC4	3q27 5984
			RFC5 (MGC1155, RFC36)	RFC5	12q24.2-q24.3 5985
β -clamp	polymerase processivity factor; interacts with MutS and may recruit it to the mismatch	PCNA complex (consists of five subunits: Rfc1, Rfc2, Rfc3, Rfc4 and Rfc5)	PCNA (MGC8367)	PCNA	20pter-p12 5111
DNA Pol III	DNA repair synthesis	DNA pol δ (consists of four subunits: POLD1 (regulatory subunit), POLD2 (catalytic subunit), POLD3 (accessory subunit) and POLD4)**	POLD1 (CDC2, POLD)	POLD1	19q13.3 5424
			POLD2	POLD2	7p13 5425
			POLD3 (K1AA0039, MGC119642, MGC119643, P66, P68)	POLD3	11q14 10714
			POLD4 (POLD5, p12)	POLD4	11q13 57804
DNA Lig1	DNA ligase; seals gap after DNA resynthesis	DNA ligase; seals gap after DNA resynthesis; ATP-dependent	LIG1 (MGC117397, MGC130025)	LIG1	19q13.2-q13.3 3978

*S. cerevisiae cells are lack of homologue of E. coli DNA Pol III; ** human cells are lack of homologue of E. coli DNA Pol III. The main DNA polymerase, Pol δ carries on the repair synthesis.

lethality and developmental defects, and eliminated cell cycle arrest and apoptosis induced by dUTPase-depletion in *C. elegans*. Therefore, it appears that dUMP misincorporation to DNA leads to checkpoint activation after processing by uracil-DNA glycosylase, and abrogation of the CLK-2 checkpoint leads to tolerance of DNA-repair intermediates (Dengg *et al.*, 2006). Furthermore, methylated nucleotides, such as 1-medATP, may be repaired by *E. coli* oxidative demethylase AlkB (Koivisto *et al.*, 2003); for a review of AlkB protein see Nieminuszczycy & Grzesiuk (this issue).

PATHWAY OF 8-oxodGTP ELIMINATION IN MAMMALIAN CELLS – MTH1, MTH2 AND NUDT5 PROTEINS

To counteract 8-oxodGTP incorporation to DNA, mammalian cells have an elaborate system of several enzymatic activities which convert this potentially mutagenic modified dNTP to its nucleoside, 8-oxodGuo (see Fig. 2). The 8-oxodGTP dephosphorylation pathways of *E. coli* and mammalian cells show some differences. In mammalian cells, like in *E. coli*, the whole process is initiated by 8-oxodGTP dephosphorylation to 8-oxodGMP by MTH1 protein, or to 8-oxodGDP probably by an unspecific nucleo-

side triphosphatase (Mo *et al.*, 1992). In contrast to *E. coli* MutT, MTH1 is unable to hydrolyze 8-oxodGDP and its 8-oxodGTPase activity is strongly inhibited by this oxidized dNDP, and also by 2-oxodADP (Bialkowski & Kasprzak, 1998; Fujikawa *et al.*, 1999). 8-OxodGDP and 2-oxodADP may be phosphorylated back to 8-oxodGTP and 2-oxodATP, respectively, by nonspecific NDPK (Hayakawa *et al.*, 1995; Kamiya & Kasai, 1999). Importantly, 8-oxodGTP can be generated only by direct oxidation of dGTP or by phosphorylation of 8-oxodGDP, and it does not come from the ribonucleotide pool, since ribonucleotide reductase, normally catalyzing the reduction of NDPs to dNDPs, cannot convert 8-oxoGDP to 8-oxodGDP (Hayakawa *et al.*, 1995).

To counteract the MTH1 inhibition by 8-oxodGDP, and to eliminate this potential 8-oxodGTP source, mammalian cells possess an enzymatic activity which hydrolyses 8-oxodGDP to 8-oxodGMP, namely the NUDT5 protein. NUDT5, originally discovered as ADP-sugar pyrophosphatase (Canales *et al.*, 1995; Kim *et al.*, 1998; Gasmi *et al.*, 1999; Yang *et al.*, 2000; Ribeiro *et al.*, 2001), dephosphorylates 8-oxodGDP with high specificity, i.e. its K_m for this substrate equals 0.77 μM (Ishibashi *et al.*, 2003). Taking into account that the K_m of hMTH1 protein for 8-oxodGTP is almost 20 times higher (i.e. it is in the range of 12.5–17.3 μM (Mo *et al.*, 1992; Fujikawa

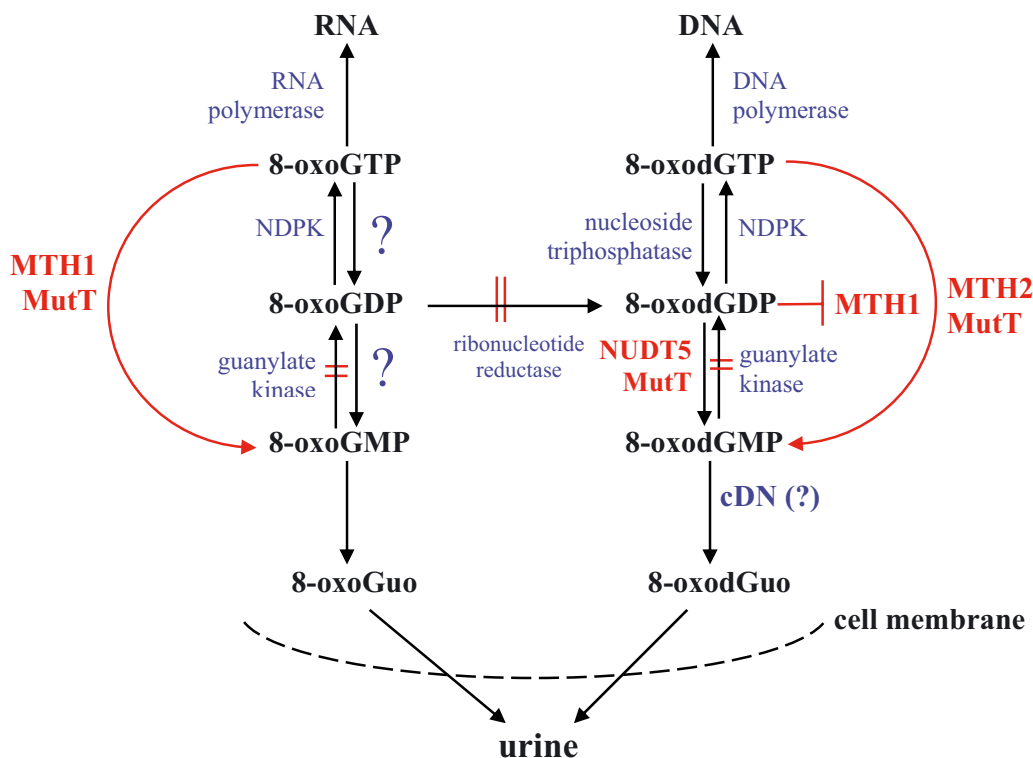


Figure 2. Pathways of interconversion of 8-oxo(d)G-containing nucleotides in *E. coli* and mammalian cells (based on Hayakawa *et al.*, 1999; Ishibashi *et al.*, 2003; 2005). Double bars represent a block of reaction.

et al., 1999), it can be concluded that NUDT5 may play a more important role than the MTH1 protein in prevention of 8-oxodGTP-induced mutations. Additionally, NUDT5 also prevents transcription errors by efficient 8-oxoGDP hydrolysis (Ishibashi *et al.*, 2003). Importantly, the dephosphorylation of 8-oxodGTP or 8-oxodGDP to 8-oxodGMP by MTH1 or NUDT5, respectively, is irreversible, since guanylate kinase, normally phosphorylating dGMP to dGDP, is inactive on 8-oxodGMP (Hayakawa *et al.*, 1995; Kim *et al.*, 2006). Finally, 8-oxodGMP is dephosphorylated to 8-oxodGuo, probably by cytoplasmic 5'(3')-deoxyribonucleotidase (cDN) (Hayakawa *et al.*, 1995). This proposed pathway of 8-oxodGTP dephosphorylation is further supported by the observation that both hMTH1 expression and nucleotide pool size were shown to significantly influence the extracellular 8-oxodGuo level (Haghdoust *et al.*, 2005; 2006). Furthermore, 8-oxodGuo is excreted to urine without further metabolism, since enzymes of purine nucleotide metabolism, which convert dGuo to uric acid, such as purine nucleoside phosphorylase (catalyzing phosphorolysis of the dGuo N-glycosidic bond with formation of guanine and deoxyribose-1-phosphate) and guanase (catalyzing deamination of guanine to xanthine) are not active on 8-oxodGuo and 8-oxoGuo, respectively (Bialkowski & Olinski, 1997). Urinary 8-oxodGuo has been proposed to be a biomarker of oxidative stress (Shigenaga *et al.*, 1989).

Although hMTH1 is functionally and structurally (Mishima *et al.*, 2004) related to its *E. coli* counterpart, it differs from MutT in its lower substrate specificity for 8-oxodGTP, with the K_m 26–216 times higher than that of the MutT protein (Mo *et al.*, 1992; Fujikawa *et al.*, 1999; Kamiya *et al.*, 2004). Interestingly, hMTH1 has been shown to have a broader substrate specificity than MutT, and it hydrolyses oxidized forms of dATP, 8-oxodATP and 2-oxodATP (Fujikawa *et al.*, 1999), and also 8-chlorodGTP-formed by HOCl modification (Fujikawa *et al.*, 2002).

Human MutT homologue (*hMTH1*) gene spans 9 kb, is localized on chromosome 7p22 (Furuichi *et al.*, 1994), and consists of five major exons, with exon 1 consisting of two segments (1a and 1b), exon 2 consisting of three segments (2a, 2b and 2c), and exons 3, 4 and 5 without segmentation. Alternative splicing results in formation of seven types of transcripts (1, 2A, 2B, 3A, 3B, 4A and 4B), with type 1 mRNA transcript predominating in most or all human cells and tissues (Oda *et al.*, 1997). All transcripts direct formation of a 156-amino-acid (18-kDa) hMTH1 protein isoform (termed p18) from the same AUG4 located at the beginning of exon 3. Additionally, B type mRNAs (2B, 3B and 4B) have three additional upstream AUGs (AUG1, AUG2 and AUG3)

localized in-frame with AUG4. AUG1 is followed by a termination codon, so functional products are produced only from AUG2, AUG3 and AUG4. Therefore, B-type mRNAs produce additionally a 171-amino-acid (p21) and a 179-amino-acid (p22) polypeptide from AUG3 and AUG2, respectively. Western blot analysis of Jurkat and HeLa cells crude extracts revealed the existence of all three isoforms of MTH1 protein (i.e. p18, p21 and p22), with the p18 isoform constituting 90%. Additionally, a single nucleotide polymorphism (SNP) is present at the 5' splice site (GT→GC) of exon 2c segment, which alters the splicing pattern of exon 2c. This polymorphism destroys the termination codon after AUG1, which generates an extended open reading frame coding for a 197-amino-acid polypeptide (p26) (Oda *et al.*, 1997). The frequency of the C allele was estimated at about 7–9% in Japanese population (Kohno *et al.*, 2006). Computer modeling revealed that p18 and p26 proteins contain a mitochondrial targeting sequence, and the additional N-terminal 18-amino-acid fragment of the p26 isoform constitutes a better mitochondria-targeting signal than that found in p18 isoform. All four hMTH1 isoforms were shown to have enzymatic activity (Sakai *et al.*, 2006). One more polymorphism was discovered in exon 4 in codon 83 of the p18 hMTH1 protein coding sequence, where GTG encoding valine is changed to ATG encoding methionine (Wu *et al.*, 1995). The Met83 variant was shown to be more thermolabile, more hydrophobic, have a higher α -helix content and lower catalytic activity than Val83 (Yakushiji *et al.*, 1997). The frequency of this type of polymorphic alteration in the *hMTH1* allele was estimated at about 9% in the Japanese population. There is a tight linkage between the two *hMTH1* polymorphic sites, Met83 and GC at exon 2c, or Val83 and GT at exon 2c, which results in the synthesis of Met83-hMTH1 (p26), but not Val83-hMTH1 (p26) (Oda *et al.*, 1999). Other polymorphisms reported for *hMTH1* are as follows: T to C at codon 45 in exon 3, with C allele frequency 2.33%, silent C to T polymorphism at codon 119 in exon 5, with T allele frequency 2.03%, C to T polymorphism in intron 3, and G to A polymorphism at position 92, resulting in the Arg31Gln change (Wu *et al.*, 1995; Sieber *et al.*, 2003; Jiang *et al.*, 2005).

hMTH1 mRNA is abundant in human thymus, testis and embryonic tissues (Oda *et al.*, 1997). In mice, the amounts of *MTH1* mRNA found in various organs were as follows: embryonic cells >> thymus, liver > large intestine > testis > kidney, spleen > stomach, lung, heart > brain (Kakuma *et al.*, 1995; Igarashi *et al.*, 1997). In human cells hMTH1 protein is localized mainly in the cytoplasm and nucleus, with 5–10% present in mitochondria (mainly in the mitochondrial matrix) (Kang *et al.*, 1995; Yoshimura *et al.*, 2003).

ROLE OF hMTH1 IN HUMAN DISEASE

It has been proposed that an early step in carcinogenesis is elevation of the rate of spontaneous mutations, i.e. development of a mutator phenotype (Loeb, 2001; Beckman & Loeb, 2006; Venkatesan *et al.*, 2006). Since MutT-deficient *E. coli* cells show a clear mutator phenotype, the *hMTH1* gene was suspected to be one of the genes whose deficiency would be involved in cancer progression. Consistently with this assumption, *MTH1*-knockout mice showed a higher incidence of lung, liver and stomach cancer (Tsuzuki *et al.*, 2001a; 2001b). However, no mutations or polymorphisms in the *hMTH1* gene were found to be correlated with hereditary nonpolyposis colorectal cancer (HNPCC) (Wu *et al.*, 1995), acute childhood leukemia (Lin *et al.*, 1998b), hepatocellular carcinoma, lung cancer (Oda *et al.*, 1999), ovarian cancer (Takama *et al.*, 2000), familial adenomatous polyposis (FAP), sporadic colorectal cancer (Sieber *et al.*, 2003; Kim *et al.*, 2004), nor with Parkinson's disease (Satoh & Kuroda, 2000). Similarly, no such correlation was found in the rat 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP)-induced mammary carcinomas, which showed an elevated level of AT→CG transversions (Okochi *et al.*, 2002a; 2002b). On the other hand, the Val83Met polymorphism is suggested to be involved in the development of type 1 diabetes mellitus in female Japanese (Miyako *et al.*, 2004), and together with the T/C polymorphism in exon 2, with the risk of small cell lung cancer (SCLC), but not with non-small cell lung cancer (NSCLC) (Kohno *et al.*, 2006). Furthermore, the Val83Met polymorphism was shown to be more frequent in gastric cancer patients, and the Met83 variant correlated with somatic mutations in *TP53* tumor suppressor gene (Kimura *et al.*, 2004).

Surprisingly, in various types of tumors and disease states, and in rodent models of human diseases, *MTH1* overexpression was found to be more common than its mutation. Thus, *MTH1* mRNA was shown to be overexpressed in renal cell carcinoma (Okamoto *et al.*, 1996), lung cancer cells and NSCLC tissues (Hibi *et al.*, 1998; Kennedy *et al.*, 1998), hepatocellular carcinoma (Zhou *et al.*, 2005), breast cancer (Wani *et al.*, 1998), PhIP-induced rat mammary carcinomas (Okochi *et al.*, 2002a; 2002b), *MTH1* protein level was shown to be increased in brain tumors (Iida *et al.*, 2001), NSCLC (Kennedy *et al.*, 2003), colorectal cancer (Koketsu *et al.*, 2004), lung epithelial cells of patients with idiopathic interstitial pneumonias (Kuwano *et al.*, 2003), mouse heart after myocardial infarction (Tsutsui *et al.*, 2001), and *hMTH1* activity was shown to be increased in NSCLC (Speina *et al.*, 2005) in comparison with non affected tissues or cells. Furthermore, *hMTH1* overexpression was also observed in regions involved in oxidative stress-in-

duced damage in brains of patients with Parkinson's (Shimura-Miura *et al.*, 1999) and Alzheimer's disease (Furuta *et al.*, 2001), in nuclei of motor neurons of patients with amyotrophic lateral sclerosis (Kikuchi *et al.*, 2002), and also was shown to protect mouse neurons from oxidative stress damage in a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine induced Parkinson's disease model (Yamaguchi *et al.*, 2006), and in kainate-induced excitotoxicity (Kajitani *et al.*, 2006). Furthermore, *MTH1* was also shown to suppress H₂O₂-induced cell death in mouse embryo fibroblasts (Yoshimura *et al.*, 2003). Consistently with the above results, *MTH1* overexpression was observed under oxidative stress induced by H₂O₂ in cultured glioma cells (Iida *et al.*, 2004), human skin fibroblasts and Jurkat cells (Meyer *et al.*, 2000), and in cells exposed to various toxic agents, such as in the case of human lung tissues of tobacco-smoking NSCLC patients (Arczewska *et al.*, in preparation), human fibroblasts exposed to ionizing radiation (Haghdoost *et al.*, 2006), in livers of rats treated with carbon tetrachloride (Takahashi *et al.*, 1998), rat lung epithelial cells treated with urban particulate matter (Choi *et al.*, 2004), human lung epithelial cells treated with crocidolite asbestos (Kim *et al.*, 2001), and also in tissues exposed to a high level of toxic metabolites excreted from the organism, such as the rat kidney inner cortex (Kasprzak *et al.*, 2001) and human colorectal cancers located in the distal part of the colon (Koketsu *et al.*, 2004). Furthermore, *hMTH1* overexpression was observed under increased oxygen consumption, i.e. in leukocytes of healthy subjects after exercises (Sato *et al.*, 2003). All the above observations have led to the conclusion that *hMTH1* overexpression is a molecular marker of oxidative stress, especially in cancer cells (Kennedy *et al.*, 1998), and was even proposed to be a marker for diagnosis of patients with non-small cell lung cancer (Chong *et al.*, 2006). In fact, *hMTH1* overexpression has proved to be a reliable marker of oxidative stress in cancer and other diseases, since a high level of its expression in peripheral lymphocytes was shown to be associated with increased risk of prostate cancer (Liu *et al.*, 2003), and its overexpression was observed in lymphocytes of uremic patients (Tarng *et al.*, 2004).

The role of *MTH1* in oxidative-damage prevention is further highlighted by the observation that *hMTH1* mRNA level is inversely correlated with 8-oxoG DNA level in human lung cancer cell lines (Kennedy *et al.*, 1998) and in leukocytes of healthy subjects after exercise (Sato *et al.*, 2003), a higher *hMTH1* mRNA level coincides with lower 8-oxoG DNA levels in human lung epithelial cells treated with crocidolite asbestos (Kim *et al.*, 2001), a higher *MTH1* activity coincides with lower 8-oxoG DNA levels in fetal compared to maternal mouse organs (Bialkowski *et al.*, 1999b), a higher *hMTH1*

protein level coincides with higher 8-oxodGuo levels in the cytoplasm and mitochondria of substantia nigra neurons of patients with Parkinson's disease (Shimura-Miura *et al.*, 1999) and the hMTH1 protein level is positively correlated with extracellular 8-oxodGuo level in cell cultures (Haghdoost *et al.*, 2006). Furthermore, treatment of rats with cadmium (II) (Cd(II)), which inhibits the activity of the MutT and MTH1 proteins (Porter *et al.*, 1997; Bialkowski & Kasprzak, 1998), resulted in a decrease of MTH1 activity concurrently with an increase of 8-oxoG level in DNA of the testis, the target organ of Cd(II)-induced mutagenesis (Bialkowski *et al.*, 1999a).

Interestingly, although MTH1 expression was found to be increased in replicating cells (Wani & D'Ambrosio, 1995), stimulated by phytohemagglutinin and interleukin-2 (Oda *et al.*, 1997), and higher in tissues with highly proliferating cells, such as thymus and testis, than in tissues with non-proliferating cells, such as brain (Kakuma *et al.*, 1995; Igarashi *et al.*, 1997; Oda *et al.*, 1997), Bialkowski and Kasprzak (2004) have shown that MTH1 protein activity is not regulated by the cell proliferation rate. Furthermore, the MTH1 protein activity does not depend on the cell cycle stage, and is not changed under serum starvation of cultured cells, but decreases with increasing cell population density (Bialkowski & Kasprzak, 2000). Therefore, although MTH1 overexpression under oxidative stress and in cancer cells is a well-recognized feature, the actual mechanisms that are involved in this phenomenon remain to be elucidated.

PREVENTION OF 8-oxoG-INDUCED MUTATIONS BY GO SYSTEM – COOPERATION OF THE hMTH1 PROTEIN AND BER PATHWAY

8-OxoG may be formed in DNA by G oxidation or by 8-oxodGTP incorporation opposite A or C (see Fig. 2). In *E. coli* 8-oxoG paired with C is removed by MutM protein, but, if unrepaired it may pair with A upon replication and thus GC→TA transversions occur. On the other hand, A is removed from the 8-oxoG•A pair by MutY protein, which prevents GC→TA transversions. Paradoxically, if 8-oxoG comes from 8-oxodGTP incorporated opposite A, then removal of A by MutY would induce AT→CG transversions, since 8-oxoG may pair with C upon replication. Therefore, the MutT protein hydrolyzing 8-oxodGTP is crucial in prevention of AT→CG transversions. Altogether, MutM, MutY and MutT were proposed to cooperate in prevention of 8-oxoG (GO)-induced mutations, and this prevention system was termed GO (Michaels & Miller, 1992). Consistently, GC→TA transitions are greatly increased in an *E. coli* *mutMmutY* double mutant, but

in the triple mutant *mutMmutYmutT* their frequency is not further increased. This phenomenon may be explained by 8-oxoG removal by Nei glycosylase (for a review see Krwawicz *et al.*, this issue) or other DNA repair systems, such as MMR (see below) or NER (Czeczot *et al.*, 1991; Bregeon *et al.*, 2003). On the other hand, *mutMmutYmutT* and *mutYmutT* show a lower level of AT→CG transversions than *mutMmutT* and *mutT*, which confirms that MutY activity in fact enhances 8-oxodGTP-induced mutagenesis (Fowler *et al.*, 2003).

Mammalian cells possess three main N-glycosylases that prevent 8-oxoG-induced mutations: OGG1, which preferentially removes 8-oxoG from pairs with C or T, OGG2, which removes 8-oxoG paired with G or A, and MYH, which removes A from the pair with 8-oxoG. Mammalian OGG2 has been proposed to remove mainly 8-oxoG incorporated from the cellular nucleotide pool (for a review see (Nakabeppu *et al.*, 2006)). Similarly like in *E. coli* cells, OGG1 and MYH are key players in GC→TA transversions prevention, and *OGG1^{-/-} MYH^{-/-}* double knockout mice show an increased level of G→T transversions together with a very high incidence of tumors (Xie *et al.*, 2004). Surprisingly, *MTH1* disruption appeared to suppress lung tumorigenesis in *OGG1*-knockout mice, which was attributed to the increased cell death of damaged tumor progenitor cells upon extensive 8-oxoG incorporation in DNA and RNA (Sakumi *et al.*, 2003).

MISMATCH REPAIR (MMR)

Mismatch repair (MMR) is the major postreplicative DNA repair system, which increases replication fidelity up to 1000-fold (Modrich & Lahue, 1996; Schofield & Hsieh, 2003). MMR removes primary replication errors that escaped DNA polymerase proofreading, such as base-base mismatches and small insertion/deletion loops (IDLs), which are most easily formed in long repetitive sequences, i.e. in microsatellites. Thus, defects in MMR induce the mutator phenotype characterized by changes in the microsatellites length, termed microsatellite instability (MSI). MSI is an established biomarker for MMR dysfunction in tumor cells (Umar *et al.*, 2004).

Additionally, MMR repairs also modified bases, such as 8-oxoG (Ni *et al.*, 1999; Mazurek *et al.*, 2002; Macpherson *et al.*, 2005), 2-oxoadenine (Barone *et al.*, 2007), carcinogen adducts (Li *et al.*, 1996), and UV-photoproducts (Feng *et al.*, 1991; Mu *et al.*, 1997; Wang *et al.*, 1999). MMR processes also natural bases paired with template *O*⁶-methylguanine, *O*⁴-methylthymine, (Duckett *et al.*, 1996; Rasmussen & Samson, 1996), 1,*N*²-propanoguanine, malondialdehyde-guanine (*M*₁G) (Johnson *et al.*, 1999) and cisplatin ad-

ducts (Duckett *et al.*, 1996; Mello *et al.*, 1996; Yamada *et al.*, 1997). This induces MMR-mediated cytotoxicity and MMR-defective cells are resistant to methylating agents and cisplatin.

Finally, MMR participates in affinity maturation of antibodies, regulation of the mitotic and meiotic recombination, DNA-damage signaling, apoptosis (reviewed in: Harfe & Jinks-Robertson, 2000; Schofield & Hsieh, 2003; Jiricny, 2006), and transcription-coupled repair (TCR) (see, for example, Lee *et al.*, 2004). Furthermore, paradoxically, rearrangements resulting in expansions of tandem trinucleotide repeats, observed in disorders such as Huntington's disease, fragile X syndrome and myotonic dystrophy, have been shown to depend on functional MMR proteins in mice (Manley *et al.*, 1999; Kovtun & McMurray, 2001; van den Broek *et al.*, 2002; Savouret *et al.*, 2003; Gomes-Pereira *et al.*, 2004), and consistently MutS β was shown to bind hairpin loops formed by such trinucleotide repeats (Owen *et al.*, 2005). Thus, in this case functional MMR rather induces genome destabilization, which may promote disease development.

Methyl-directed MMR in *E. coli*

Key players in the *E. coli* MMR system, MutS, MutL, MutH and UvrD were identified in studies of mutator strains (Cox *et al.*, 1972; Wagner & Meselson, 1976), and the whole system was reconstituted *in vitro* (Lahue *et al.*, 1989). MMR preferentially repairs the newly synthesized strand, and in *E. coli* strand discrimination is based on the fact that adenine is methylated in GATC sequences by Dam methyltransferase about 2 min after DNA synthesis, therefore the newly synthesized strand is transiently unmethylated (Lyons & Schendel, 1984). Consistently with its role in MMR, *dam E. coli* cells are weak mutators (Glickman, 1979).

Initially, MutS protein dimer (or tetramer) recognizes and binds IDLs containing up to about four unpaired bases (Parker & Marinus, 1992), and also seven of eight possible mismatches (Su & Modrich, 1986; Su *et al.*, 1988). MutS binding affinities and mismatch repair efficiencies vary with the composition of the mismatch and local sequence context, with G•T and C•A mismatches being preferentially repaired in most of the tested systems (Kramer *et al.*, 1984; Dohet *et al.*, 1985; Jones *et al.*, 1987; Brown *et al.*, 2001). Consistently, defects in MMR genes induce mainly GC→AT and AT→GC transitions, and frameshift mutations (Lahue *et al.*, 1989). The C•C mismatch is almost not recognized by MutS and it was postulated to be repaired by an MMR-independent pathway (Nakahara *et al.*, 2000). Further, mismatch-bound MutS recruits MutL dimer in an ATP-dependent manner (Grilley *et al.*, 1989). The

MutL protein is an ATPase and is thought to be a "molecular matchmaker" which mediates the interaction between MutS and MutH (Modrich, 1991). Thus formed, the ternary complex of MutS(ATP)–MutL–mismatch activates monomeric MutH endonuclease which incises an unmethylated GATC sequence at a site 5' or 3' to the mismatch, located even 1000 bp from the mismatch (Welsh *et al.*, 1987; Bruni *et al.*, 1988). The resulting nick serves as the point of entry for MutL-activated UvrD helicase, which unwinds DNA double helix from the nick to about 100 nucleotides past the mismatch, and single-stranded DNA binding (SSB) protein, which stabilizes the single-stranded gap (Lahue *et al.*, 1989). After unwinding the ssDNA flap is degraded in the 5'→3' direction by ExoVII or RecJ exonuclease, if the incision occurred 5' to the mismatch, or in the 3'→5' direction by ExoI, ExoVII or Exo X exonuclease, if the incision occurred 3' to the mismatch (Cooper *et al.*, 1993; Grilley *et al.*, 1993; Burdett *et al.*, 2001). Finally, the SSB-stabilized single-stranded gap is filled in by DNA polymerase III holoenzyme and DNA ends are sealed by LigI. Importantly, β clamp, which is a polymerase processivity factor, and γ complex, which loads β clamp onto the DNA helix are required for MMR *in vitro* (Lahue *et al.*, 1989), and β clamp was shown to interact with MutS (Lopez de Saro & O'Donnell, 2001).

MMR in eukaryotes

In eukaryotes several homologs of MutS and MutL have been identified, including six *mutS* homologues (*MSH1–MSH6*) and four *mutL* homologues (*MLH1–MLH3*, and *PMS1*) found in yeast (Kramer *et al.*, 1989; Reenan & Kolodner, 1992a; 1992b; New *et al.*, 1993; Prolla *et al.*, 1994; Ross-Macdonald & Roeder, 1994; Hollingsworth *et al.*, 1995; Marsischky *et al.*, 1996), and five *mutS* (*MSH2–MSH6*) and four *mutL* (*MLH1*, *MLH3*, *PMS1*, and *PMS2*) homologues found in mammals (Hughes & Jiricny, 1992; Fishel *et al.*, 1993; Leach *et al.*, 1993; Bronner *et al.*, 1994; Nicolaides *et al.*, 1994; Papadopoulos *et al.*, 1994; Liu *et al.*, 1994; Varlet *et al.*, 1994; Horii *et al.*, 1994; Drummond *et al.*, 1995; Li & Modrich, 1995; Palombo *et al.*, 1995; Baker *et al.*, 1995; Acharya *et al.*, 1996; Watanabe *et al.*, 1996; Paquis-Flucklinger *et al.*, 1997; Her & Doggett, 1998; Winand *et al.*, 1998; Lipkin *et al.*, 2000).

Although MutS and MutL proteins are evolutionarily conserved, the MutH endonuclease is restricted only to Gram-negative bacteria (Jiricny, 2006). Thus, in eukaryotic cells the signals that direct MMR to the newly synthesized strand remain uncertain. Initially it has been proposed that strands are discriminated on the basis of cytosine methylation, analogously to the role of adenine methylation in *E. coli* cells, but this hypothesis has not been veri-

fied (Drummond & Bellacosa, 2001; Petranovic *et al.*, 2000). More plausible hypotheses suggest that natural single-strand breaks, occurring as replication intermediates, the replication complex, especially proliferating cell nuclear antigen (PCNA), or proteins segregating with individual strands after replication may be involved. This was supported by the observation that *mutH* *E. coli* strains are able to carry out MutH-independent MMR, both *in vivo* and *in vitro*, from a single-strand break located at the vicinity of the mismatch (Lahue *et al.*, 1989; Kramer *et al.*, 1984; Bruni *et al.*, 1988). The same was observed in human *in vitro* MMR assays (Holmes *et al.*, 1990; Thomas *et al.*, 1991; Iams *et al.*, 2002). Furthermore, similarly as observed in *E. coli*, the eukaryotic β clamp counterpart — PCNA — interacts with yeast and human MutS and MutL homologues (Umar *et al.*, 1996; Clark *et al.*, 2000; Flores-Rozas *et al.*, 2000; Kleczkowska *et al.*, 2001), and mutations in PCNA that abolish interaction with MSH3 and MSH6 confer partial mutator phenotype *in vivo* (Johnson *et al.*, 1996; Chen *et al.*, 1999; Clark *et al.*, 2000; Flores-Rozas *et al.*, 2000; Lau *et al.*, 2002; Lau & Kolodner, 2003). Thus, PCNA is implicated not only in gap filling repair synthesis, but also in early stages of MMR (Umar *et al.*, 1996; Gu *et al.*, 1998). Moreover, PCNA and eukaryotic clamp loader replication factor ζ (RFC) were shown to be essential for bi-directional excision during MMR (Dzantiev *et al.*, 2004). Human MSH2 and MSH3 interact also with MMR exonuclease — Exo1 (Schmutte *et al.*, 1998; 2001; Rasmussen *et al.*, 2000).

Eukaryotic MMR proteins function as heterodimers. MSH2-MSH6 form a heterodimer, termed MutS α , which recognizes all eight single base mismatches, including C•C mismatch, and small IDLs, up to about 10 unpaired nucleotides, whereas the MSH2-MSH3 heterodimer (MutS β) recognizes IDLs containing from 2 up to 16 nucleotides (McCulloch *et al.*, 2003). In human cells the MutS α to MutS β ratio is roughly 6:1 (Drummond *et al.*, 1995; 1997; Palombo *et al.*, 1995; 1996; Acharya *et al.*, 1996; Genschel *et al.*, 1998; Umar *et al.*, 1998). Consistently, MSH6-deficient tumor cells show mononucleotide (but not dinucleotide) instability (Kolodner *et al.*, 1999; Verma *et al.*, 1999), and MSH3-deficient cells do not display microsatellite instability (Inokuchi *et al.*, 1995). Mammalian MSH4 and MSH5 also form a heterodimer, show germ cell-specific expression and are involved in meiotic recombination, but not postreplicative MMR (Ross-Macdonald & Roeder, 1994; Bocker *et al.*, 1999; Kneitz *et al.*, 2000; Snowden *et al.*, 2004). MutS α forms an ATP-dependent sliding clamp, but it is still not evident if the movement of MutS α on DNA is driven by ATP hydrolysis (Blackwell *et al.*, 1998), or is ATP hydrolysis-independent (Gradia *et al.*, 1997) (Fig. 3; for discussion of the proposed models see: Kunkel & Erie, 2005; Iyer *et al.*, 2006; Jiricny, 2006).

Next, MutS α (or MutS β) recruits MutL α ATPase (MLH1-PMS2 heterodimer; in yeast MLH1-PMS1 heterodimer) (Li & Modrich, 1995), and MutS α -MutL α complexes may travel along the DNA helix, similarly to the MutS α sliding clamp (Blackwell *et al.*, 2001). MutL α has been proposed to be important for coupling mismatch recognition with further MMR steps and consistently it interacts with Exo1 (Schmutte *et al.*, 2001; Tran *et al.*, 2001) and PCNA (Umar *et al.*, 1996; Lee & Alani, 2006). Importantly, MutL α deficiency leads to the mutator phenotype and MSI, as observed in sporadic colorectal or endometrial cancers with epigenetic silencing of MLH1 expression (Kane *et al.*, 1997; Cunningham *et al.*, 1998; Esteller *et al.*, 1998; Herman *et al.*, 1998; Veigl *et al.*, 1998; Wheeler *et al.*, 1999). Moreover, several MLH1 mutations found in hereditary non-polyposis colorectal cancer (HNPCC) patients were found to reduce interaction with Exo1 (Schmutte *et al.*, 2001). Other mammalian MutL homologues also function in heterodimers. MLH1 and PMS1 form the MutL β heterodimer whose function is still unknown, but PMS1-knockout mice exhibit MSI at mononucleotide runs (Prolla *et al.*, 1998), which may suggest that MutL β is somehow involved in MMR. Moreover, MLH1 and MLH3 form the MutL γ heterodimer which is thought to participate in the repair of base-base mismatches and single-nucleotide IDLs (Cannavo *et al.*, 2005), and murine cells with MLH3 deficiency display the MSI phenotype (Lipkin *et al.*, 2000). MutL γ is also involved in meiotic recombination (Santucci-Darmanin *et al.*, 2000; Lipkin *et al.*, 2002; Svetlanov & Cohen, 2004). One more protein engaged in MMR is high-mobility group box 1 (HMGB1) protein, which was shown to interact with MutS α and is required prior to the excision step (Yuan *et al.*, 2004).

Final steps of MMR include mismatch excision and DNA resynthesis. When a single-strand break is localized at the 5' side of the mismatch, Exo1, stimulated by MutS α hydrolyzes DNA in the 5'→3' direction in an ATP-, mismatch-, and replication protein A (RPA)-dependent manner (Lin *et al.*, 1998a; Genschel *et al.*, 2002; Lee Bi *et al.*, 2002). RPA plays a role similar to *E. coli* SSB, since it protects ssDNA from incision by nucleases (Ramilo *et al.*, 2002). Furthermore, eukaryotic MMR is apparently helicase-independent (Bennett *et al.*, 1997; Langland *et al.*, 2001; Pedrazzi *et al.*, 2001), and thus RPA binding has been proposed to play some role in DNA unwinding. Exo1 is the only eukaryotic MMR exonuclease, and Exo1-deficient mice are prone to lymphomas and exhibit MSI, as well as the mutator phenotype (Wei *et al.*, 2003; Tran *et al.*, 2004). The single stranded gap is stabilized by RPA. RPA reduces Exo1 processivity by binding ssDNA, and Exo1 is further inhibited by MutS α and MutL α upon reaching the mismatch. This leads to termination of excision. In consequence

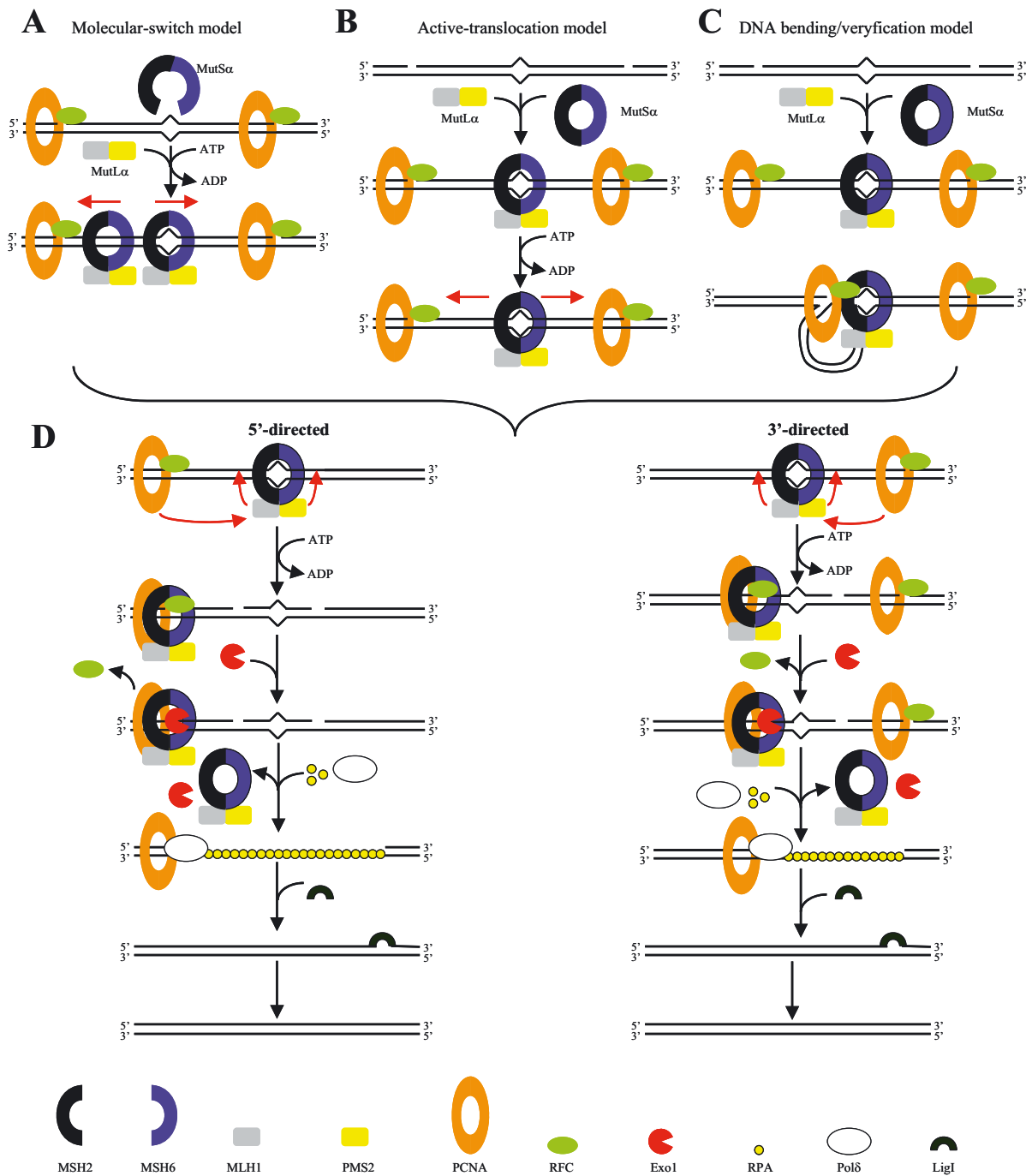


Figure 3. Models of MMR complex assembly (A, B and C) and mismatch excision (D).

(A) In the molecular-switch model (Gradia *et al.*, 1999) MutS α normally exists in ADP-bound form, and upon mismatch binding ADP is exchanged to ATP, which induces conformational changes and ATP-independent diffusion of multiple MutS α (possibly in complex with MutL α) sliding clamps along DNA helix. (B) In the active-translocation model (Blackwell *et al.*, 1998; Martik *et al.*, 2004), MutS α clamp (possibly in complex with MutL α) translocates along DNA and ATP is used as energy source to drive its motion. (C) In the DNA bending/verification model (Wang & Hays, 2003; 2004) MutS α remains at the mismatch and makes contact with strand break through DNA bending. MutS is able to sense the mismatch, and when bound to DNA without mismatch it hydrolyzes ATP and in consequence becomes displaced from the DNA. On the other hand, when MutS binds DNA containing mismatch, ATP is not hydrolyzed, what leads to activation of downstream MMR effectors. (D) When MutS α -MutL α complex comes into contact with PCNA and RFC bound to strand break, it triggers further MMR steps. MutS α , PCNA and RFC activate latent MutL α endonuclease (Kadyrov *et al.*, 2006), which cleaves DNA at both sides of the mismatch in ATP-dependent manner. Next, at the 5'-break (created by MutL α endonucleolytic cleavage or preexisting in DNA) MutS α -MutL α complex displaces RFC from complex with PCNA and loads Exo1, which hydrolyzes DNA in 5' \rightarrow 3' direction. The single stranded gap is stabilized by RPA. RPA reduces Exo1 processivity by binding ssDNA, and Exo1 is further inhibited by MutS α and MutL α upon reaching the mismatch. This leads to termination of excision. Finally, gap is filled by Pol δ , in presence of PCNA and RPA, and ends are joined by LigI.

excision terminates at about 100 nucleotides beyond the mismatch (Genschel & Modrich, 2003; Nielsen *et al.*, 2004). However, Exo1 lacks the 3'→5' exonuclease activity, and a complex consisting of MutS α , MutL α , PCNA, Exo1, and RFC is essential for MMR from a single-strand break located at the 3' side of the mismatch (Dzantiev *et al.*, 2004; Guo *et al.*, 2004). RFC has been proposed to play a double role in 3'-directed excision: it loads the PCNA clamp, but also suppresses 5'→3' excision by Exo1 from a single-strand break located 3' to the mismatch (Dzantiev *et al.*, 2004). It has been proposed that 3'→5' excision is mediated by Pol δ or Pol ϵ proofreading activity, which was supported by genetic and biochemical inhibition studies conducted *in vivo* in *S. cerevisiae* and *in vitro* with HeLa extracts (Tran *et al.*, 1999; Wang & Hays, 2002). The recent discovery that MutL α has an endonuclease activity, stimulated by MMR cofactors (MutS α , MutL α , PCNA, RFC, ATP and divalent cations) (Kadyrov *et al.*, 2006) may explain the MMR mechanism in a situation when the single strand break is located at the 3' side of the mismatch. Thus, the 5' nick introduced by this endonuclease activity specifically in the discontinuous strand may serve for Exo1 degradation in substrates containing a break localized 3' to the mismatch. Finally, DNA polymerase δ fills the gap, in the presence of PCNA (Gu *et al.*, 1998) and RPA (Lin *et al.*, 1998a; Ramilo *et al.*, 2002), and finally DNA ligase (probably LIG1) seals the ends (Constantin *et al.*, 2005; Zhang *et al.*, 2005).

MMR and hereditary non-polyposis colorectal cancer (HNPCC)

Defects in MMR are implicated in hereditary non-polyposis colorectal cancer (HNPCC), also termed Lynch syndrome, and less frequently in endometrial, ovarian, gastric and some other cancer forms. Colon epithelium has the highest known proliferation rate of all cell types, and this may directly contribute to the accumulation of MMR-deficiency-induced replication errors specifically in this tissue type. Lynch syndrome accounts for about 5–8% of all colon cancer cases. About 500 different Lynch syndrome-associated MMR gene mutations have been found, and among them *MLH1*, *MSH2*, and *MSH6* gene mutations constitute about 50%, 40%, and 10%, respectively (for mutations found in respective genes see <http://www.insight-group.org/>). Mutations in *MSH6* show stronger association with endometrial than colon cancer (Wijnen *et al.*, 1999). Mice defective in either *MLH1*, *MSH2* or *MSH6* show cancer susceptibility and develop mainly lymphomas, gastrointestinal (GI) epithelial adenomas or basal cell carcinomas, whereas *PMS2*^{-/-} mice develop lymphomas and sarcomas, but not GI tumors. Moreover, a few pathogenic germline muta-

tions have been found in *PMS2* and most of them are associated with Turcot syndrome, characterized by brain tumors, colonic polyps and colon cancer. Finally, mutations in *MLH3* may also be associated with Lynch syndrome. On the other hand, although *MSH3* frequently shows somatic mutations in MSI-positive tumors, and potentiates the consequences of defects in other MMR genes, *MSH3*-deficient mice are not cancer prone and no Lynch syndrome-associated germline mutations have been found in *MSH3* (Lynch & de la Chapelle, 1999; Peltomaki, 2005; Chao & Lipkin, 2006).

Microsatellite instability (MSI) is found in virtually all Lynch syndrome cases (Aaltonen *et al.*, 1994), and thus is a diagnostic feature for Lynch syndrome. However, MSI also appears in sporadic (i.e. non-Lynch syndrome) colon cancers, where hypermethylation of *MLH1* promoter leads to gene silencing (Kane *et al.*, 1997; Cunningham *et al.*, 1998; Esteller *et al.*, 1998; Herman *et al.*, 1998; Veigl *et al.*, 1998; Wheeler *et al.*, 1999). Thus, although 12–15% of colon cancers show MSI, only 20–25% of MSI-positive colon cancers represent Lynch syndrome, which complicates diagnosis (Lynch & de la Chapelle, 1999; Umar *et al.*, 2004; Jass, 2006).

COOPERATION BETWEEN hMTH1 PROTEIN AND MMR

The antimutagenic role of MTH1 is less pronounced than that of the MutT protein, since while the *mutT E. coli* mutant has a specifically increased level of spontaneous mutations by 100- to 10000-fold, their level in the *Hprt* locus of homozygous *MTH1*^{-/-} mouse cells is increased only 2 times in comparison with the wild type *MTH1*^{+/+} mouse cells (Tsuzuki *et al.*, 2001a; 2001b). This low level of spontaneous mutations can be explained, at least partially, by the existence of MutT homologue 2 (MTH2) protein, which is active on 8-oxodGTP and may backup MTH1 function (Cai *et al.*, 2003), and by the existence of NUDT5 protein. Importantly, both proteins, i.e. mouse MTH2 and human NUDT5 expressed in the *mutT E. coli* strain suppressed its mutator phenotype (Cai *et al.*, 2003; Ishibashi *et al.*, 2003). Furthermore, mutagenesis may be prevented by efficient removal of oxidized bases incorporated from the cellular dNTP pool by DNA repair systems, such as BER, MMR or NER. Interestingly, although the *MTH1*^{-/-} mice showed a higher incidence of lung, liver and stomach cancer (Tsuzuki *et al.*, 2001a; 2001b), they did not show an increased frequency of spontaneous *rpsL*⁻ forward mutations in comparison with the wild type *MTH1*^{+/+} mice. On the other hand, the frequency of AT→CG transversions was 3.6-times higher, and of single-base frameshifts at mononucleotide runs 5.7-times

higher in *MTH1*^{-/-} than in *MTH1*^{+/+} mice (Egashira *et al.*, 2002). Single-base frameshifts at mononucleotide runs are a characteristic feature of MMR deficiency, and MMR was in fact shown to remove 8-oxodGMP incorporated from the nucleotide pool, since overexpression of hMTH1 reduced the DNA 8-oxoG level in *MSH2*^{-/-} cells (i.e. MMR-defective) (Colussi *et al.*, 2002; Russo *et al.*, 2004). Furthermore, *MTH1*^{-/-} *MSH2*^{-/-} mice in comparison with *MSH2*^{-/-} once had a specifically increased occurrence of GC→TA transversions, which could be induced by 2-oxodAMP incorporation opposite G, or by erroneous incorporation of dAMP opposite 8-oxoG present in DNA (Egashira *et al.*, 2002). Moreover, hMTH1 overexpression reduced the level of spontaneous *Hprt* locus mutations in the *MSH2*^{-/-} background, and among them the highest reduction was observed in the case of frameshifts, AT→GC transitions and AT→TA and GC→TA transversions (Russo *et al.*, 2004). The AT→TA and GC→TA transversions are induced by erroneous incorporation of dAMP and dCMP, respectively, opposite template 2-oxoA (Kamiya & Kasai, 1997a; 1997b; Barone *et al.*, 2007). Consistently, MMR could be involved in 2-oxoA removal, since MutS α has been shown to bind 2-oxoA-containing DNA (Barone *et al.*, 2007). Therefore, the low level of spontaneous mutations in *MTH1*^{-/-} mice and mouse cultured cells can be attributed partially to the removal, by the MMR system, of oxidized bases incor-

porated from the nucleotide pool. Furthermore, in the *MTH1*^{-/-} background the high level of oxidized bases incorporated to DNA from the nucleotide pool may partially sequester MMR, leading to a more frequent occurrence of single-base frameshifts at mononucleotide runs (Egashira *et al.*, 2002). Surprisingly, AT→CG transversions, which are dramatically increased in *mutT E. coli* cells, were only slightly increased in *MTH1*^{-/-} mice (Egashira *et al.*, 2002), and only slightly decreased by hMTH1 overexpression in *MSH2*^{-/-} mice (Russo *et al.*, 2004). AT→CG transversions are induced by 8-oxodGMP incorporation opposite template A, and in *mutT E. coli* cells, lacking the MutT protein which removes both 8-oxodGTP and 8-oxodGDP, they can be much more frequent than in *MTH1*^{-/-} cells, lacking the 8-oxodGTP-hydrolysing MTH1 protein, but still possessing the MTH2 and NUDT5 proteins dephosphorylating 8-oxodGTP and 8-oxodGDP, respectively. On the other hand, *MTH1*^{-/-} mice showed increased levels of all types of mutations connected with 2-oxoA, consistently with the fact that human MTH1 hydrolyses 2-oxodATP (Russo *et al.*, 2004). This may suggest that MTH1 is the only protein specifically involved in 2-oxodATP elimination from the mammalian cellular nucleotide pool or that 2-oxoA repair by MYH glycosylase (Ohtsubo *et al.*, 2000) or MMR is saturated upon MTH1 deficiency.

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