ANTIOXIDANTS & REDOX SIGNALING
Volume 3, Number 4, 2001
Mary Ann Liebert, Inc.

Forum Review

The *OGG1* Gene Encodes a Repair Enzyme for Oxidatively Damaged DNA and Is Involved in Human Carcinogenesis

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ABSTRACT

8-Hydroxyguanine (oh^{8}G) is a major base lesion produced by reactive oxygen species. oh^{8}G in DNA causes G:C to T:A transversions and, thus, could be responsible for mutations that lead to carcinogenesis. A human DNA glycosylase/AP lyase encoded by the *OGG1* gene has an activity to remove directly oh^{8}G from DNA, and suppresses the mutagenic effect of oh^{8}G. OGG1 protein has a helix–hairpin–helix–GPD motif as a domain for both DNA binding and catalysis, a nuclear localization signal, and a mitochondria targeting signal. Among multiple OGG1 isoforms, OGG1-type 1a is expressed predominantly in human cells and repairs chromosomal DNA in the nucleus. Inactivation of the *OGG1* gene in yeast and mice leads to elevated spontaneous mutation frequency in the cells. The human *OGG1* gene maps to chromosome 3p26.2, and allelic deletions of this region occur frequently in a variety of human cancers. Moreover, the *OGG1* gene is somatically mutated in some cancer cells and is highly polymorphic among human populations. Repair activities of some mutated and polymorphic OGG1 proteins are lower than those of wild-type OGG1-type 1a-Ser326 protein and, thus, could be involved in human carcinogenesis. Antioxid. Redox Signal. 3, 597–609.

INTRODUCTION

8-HYDROXYGUANINE (oh^{8}G) is a major form of oxidative DNA damage produced by reactive free radicals (32). The presence of oh^{8}G in DNA is thought to be a major cause of G:C to T:A transversion, because oh^{8}G directs the incorporation of adenine as well as cytosine opposite the lesion (59). Thus, oh^{8}G is a highly mutagenic DNA lesion *in vivo* (15, 47) unless repaired prior to DNA replication. It has been well accepted that cancer is attributed to the accumulation of multiple genetic alterations in cells, and that oncogenes and tumor suppressor genes play a central role in the development of human cancers (75). Point mutation is one of the mechanisms that activates oncogenes and inactivates tumor suppressor genes. As G:C to T:A transversions occur frequently in several tumor suppressor genes and oncogenes, such as *p53* and *K-ras* (25), the increase of the oh^{8}G content could be a factor to increase the occurrence of such a mutation in cells. Thus, repair activities for oh^{8}G in cells are considered to be associated with the risk for G:C to T:A transversions that occur in cells and lead to carcinogenesis.

To prevent the mutagenic effect of oh^{8}G, three DNA repair genes, *MutM*, *MutY*, and *MutT*, exist in *Escherichia coli* (*E. coli*) (2, 5, 11, 43, 44, 70), and three genes, *OGG1*, *MYH*, and *MTH*, are present in human cells (1, 3, 9, 23, 42,

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53, 56, 57, 60, 63–65, 68). The bacterial *MutM* gene and the human *OGG1* gene have a function to remove oh^{8}G directly from the oh^{8}G:C base pair in double-stranded DNA (1, 3, 9, 12, 42, 56, 57, 70). In addition to these genes, transcription-coupled repair genes and mismatch repair genes have been suggested to be involved in the oh^{8}G repair (18, 39, 40, 50). However, as *Ogg1*-deficient cells derived from *Ogg1*$^{-/-}$ mice completely abolish the repair activity for oh^{8}G in a nontranscribed DNA sequence (39) and *Ogg*$^{1-/-}$ mice exhibit elevated spontaneous mutation frequency in nonproliferative tissues compared with wild-type mice (34, 45), OGG1 protein should be indispensable for the repair of oh^{8}G and the control of mutation rate in mammalian cells. In this article, we summarize the molecular characteristics and biochemical/biological functions of the *OGG1* gene and its product. We will also discuss the possible involvement of the *OGG1* gene in human carcinogenesis.

REPAIR ACTIVITIES OF OGG1 PROTEIN AGAINST oh^{8}G IN DOUBLE-STRANDED DNA

Isolation of the OGG1 *gene and oh^{8}G repair activity of its product*

As a gene for the repair enzyme for the oh^{8}G:C base pair in double-stranded DNA, *MutM* was cloned from the bacterial genome and *OGG1* was cloned from the yeast genome (11, 48, 72). Surprisingly, the bacterial *MutM* gene and the yeast *OGG1* gene did not have any significant structural homology to each other (48, 72). Recently, a structural human homologue of the yeast *OGG1* gene was cloned, and it was shown that the human gene is not only a structural homologue, but also a functional homologue of the yeast *OGG1* gene (1, 3, 9, 42, 56, 57, 60). The predicted human OGG1 protein has 345 amino acids and shares 38% amino acid identity with yeast OGG1 protein. The human *OGG1* gene was ubiquitously expressed in a variety of human organs and mapped to 3p26.2 (3, 42, 56, 57).

Human OGG1 protein efficiently catalyzes the DNA glycosylase and apurinic/apyrimidinic (AP) lyase reactions for oh^{8}G:C, oh^{8}G:T, and 2,6-diamino-4-hydroxy-5-*N*-methylformamidopyrimidine:C base pairs in double-stranded DNA (1, 4, 9, 42, 56, 57, 60). Efficient excision of oh^{8}G and 2,6-diamino-4-hydroxyformamidopyrimidine from DNA exposed to γ-irradiation was also reported (20). By using mouse OGG1 protein, it was also shown that 8-oxo-7,8-dihydrohypoxanthine:C, 8-oxo-7,8-dihydro-6-*O*-methylguanine:C, and 8-oxo-7,8-dihydroadenine:C are good substrates of OGG1 protein (80). A recent study using mouse OGG1 protein suggests that the protein catalyzes DNA glycoslyase and AP lyase reactions at different rates (80). When comparing the kinetic parameters of oh^{8}G release and DNA strand nicking, the catalytic efficiency (k_{cat}/K_m) of the AP lyase reaction was significantly lower than that of the DNA glycosylase reaction, suggesting a two-stage kinetic mechanism for mouse OGG1 protein.

After nicking the 3′ side of the AP site by the AP lyase activity of OGG1 protein, the resultant 3′-blocking end is suggested to be removed by the 3′-phosphodiesterase activity of APEX protein (Fig. 1) (21). Subsequently, a single-nucleotide gap is filled by DNA polymerase β protein, followed by ligation by Ligase III protein in a complex with XRCC1 protein (38). This oh^{8}G repair pathway corresponds to a short patch excision repair. In fact, in a study with human cell-free extracts, oh^{8}G is eliminated preferentially by the short patch repair pathway (22).

Differences in the mode of oh^{8}G repair between MutM and OGG1 proteins

There are several differences in the mode of oh^{8}G repair between *E. coli* MutM and eukaryotic OGG1 proteins. First, DNA cleavage sites are different between them (Fig. 1). MutM protein catalyzes δ-elimination reaction as well as β-elimination reaction (8, 79). Therefore, not only the 3′ side, but also the 5′ side, of the AP site is cleaved. In contrast, the 5′-nicking activity of OGG1 protein is extremely low (or none) (1, 9, 42, 56, 57, 60). After DNA cleavage by MutM protein, the 3′-blocking end is removed by the 3′-repair diesterase activity of Exonuclease III or Endonuclease IV protein

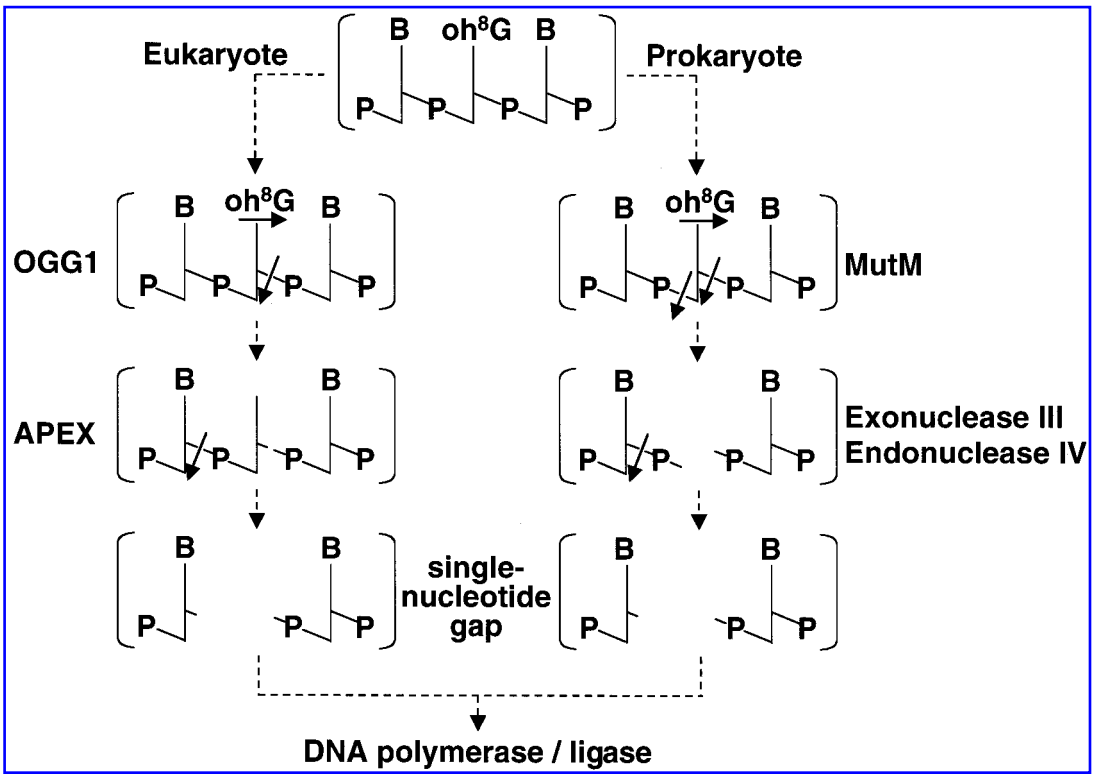

FIG. 1. Pathway of excision repair for oh^{8}G in double-stranded DNA in eukaryotic and prokaryotic cells. Arrows indicate the incision of *N*-glycosidic bond or phosphodiester bond.

(38). Thus, as in the case of a eukaryotic system, a single-nucleotide gap is formed by two-step enzymatic reactions. The second difference is the substrate specificity. MutM protein efficiently excises oh^{8}G opposite cytosine, thymine, and guanine, whereas oh^{8}G opposite guanine is less excised by OGG1 protein (1, 4, 9, 42, 56, 57, 60). Third is the kinetic mechanism. In the study by Williams and David (74), MutM protein catalyzes DNA glycosylase and AP lyase reactions at similar rates. However, in the case of mouse OGG1 protein, there is a difference in the catalytic efficiency between those reactions (80). Fourth is the difference in the kinetic constant for the oh^{8}G DNA substrate. The catalytic efficiency of AP lyase reaction by OGG1 protein is ~80-fold lower than that by MutM protein (4). However, the catalytic constant of DNA glycosylase reaction was not compared between these proteins in that study. Although MutM and OGG1 proteins are functionally similar, structural differences between them probably cause these distinct repair activities.

Activity to suppress spontaneous mutation by OGG1 protein

From several points of view, the ability of OGG1 protein to suppress spontaneous mutagenesis has been investigated. An *E. coli mutM mutY* mutant has a mutator phenotype and is deficient in oh^{8}G repair (44). Expression of OGG1 proteins suppresses the mutator phenotype of the mutant (1, 3, 9, 55–58, 69, 72). An *ogg1*-disrupted yeast strain exhibits a mutator phenotype (71). When comparing the mutation frequency by a detection system of canavanine-resistant mutants or Lys$^+$ revertants, the frequency of the *ogg1*-disrupted strain was ~10-fold higher than that of a wild-type strain. Moreover, the *ogg1*-deficient strain displayed a 50-fold increase in spontaneously occurring G:C to T:A transversions compared with the wild-type strain. In *Ogg1* null mice, the spontaneous mutation frequency in nonproliferative tissues is elevated two to three times, compared with wild-type mice in the *lacI* or *gpt* transgene-based assay system (34, 45). More-

over, like the yeast *ogg1*-disruptant, G:C to T:A transversions occur more frequently in *Ogg1* null mice than in wild-type mice. Senescence-accelerated mouse (SAM) strains with senescence-prone phenotypes have a shorter life span and earlier manifestation of various aging signs than SAM strains with senescence-resistant phenotypes. The mutation rate in a senescence-prone strain was more rapidly increased by age than that in a senescence-resistant strain, and a single base mutation was detected in the *OGG1* gene of the senescence- prone strain, which causes thermolability and catalytic dysfunction of this enzyme (17, 52). Therefore, the impaired repair activity of OGG1 protein was suggested to be a factor contributing to the high somatic mutation rate and accelerated senescence observed in the senescence-prone strains. These results indicate that OGG1 protein is an important factor in defining the mutation rate in human cells.

Stimulation of AP lyase activity

There are two classes of DNA glycosylases in eukaryotes (41). One has only glycosylase activity, and the other has glycosylase activity with AP lyase activity. OGG1 protein belongs to the latter group, as does NTHL1 protein. As these proteins possess AP lyase activity, a short patch repair pathway would be primarily involved in the repair of damaged bases. Interestingly, XPG nucleotide excision repair protein stimulates the AP lyase activity of NTHL1 protein, but not of OGG1 protein (33). Considering the lower AP lyase activity of OGG1 protein compared with the DNA glycosylase activity of the protein (80), some proteins to stimulate the AP lyase activity of OGG1 protein might exist in mammalian cells.

MUTAGENICITY OF oh^{8}G IN DOUBLE-STRANDED DNA

When oh^{8}G in double-stranded DNA has not been repaired prior to DNA replication under the conditions of lower oh^{8}G repair capacity of cells, which base is preferentially incorporated opposite oh^{8}G is a critical problem. Several human DNA polymerases possess the ability to replicate DNA containing oh^{8}G (Fig. 2). Polδ rotein, a major replicative DNA polymerase, primarily incorporates adenine opposite oh^{8}G; however, in this case, some cytosine is also inserted (59). Besides Polδ, Polη and Polκ proteins have been shown to facilitate translesion replication of oh^{8}G *in vitro* (27, 78). Polη protein preferentially inserts cytosine opposite oh^{8}G, whereas Polκ protein preferentially inserts adenine opposite the lesion. To date, the efficiency for the incorporation of adenine, cytosine, or other residues opposite oh^{8}G lesion by total polymerase activity in cells has not been fully understood. However, it is likely that the oh^{8}G:A base pair is generated through the first DNA replication and translesion syn-

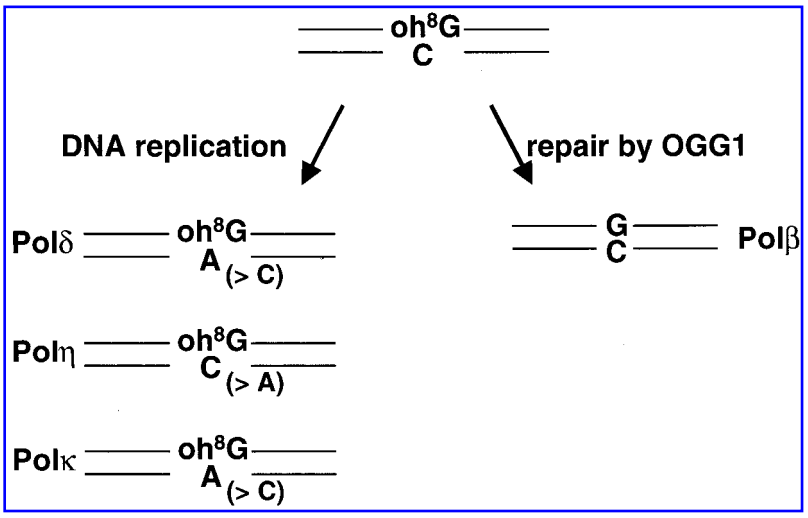

FIG. 2. Roles of DNA polymerases (Polδ, Polη, Polκ, and Polβ) in replication and repair of oh^{8}G. > indicates the preference of incorporated base.

thesis, in addition to the oh^{8}G:C base pair, and induces G:C to T:A transversion unless adenine is repaired prior to the second DNA replication. As another aspect, it is known that a 3′-blocking end generated by AP lyase activity of OGG1 protein causes the double-strand DNA break, unless removed by APEX protein prior to DNA replication. Some pathways of the double-strand break repair have a high mutagenic potential (54). Thus, the low oh^{8}G repair capacity and the imbalance in the amounts of proteins involved in the oh^{8}G repair could be critical for induction of mutations in the cells.

STRUCTURAL CHARACTERISTICS OF OGG1 PROTEIN

Conserved domains among eukaryotic OGG1 proteins

Up to the present, the *OGG1* gene has been cloned from the human, mouse, rat, yeast, and *Methanococcus jannaschii* genomes (Fig. 3) (1, 3, 9, 24, 42, 48, 55–58, 69, 72). Although the homology between the human and yeast *OGG1* gene is not so high (38% at the amino acid level), the mouse and rat *OGG*1 genes are highly homologous to the human *OGG1* gene (85.4% and 84.7% at the amino acid level). There are several domains conserved among the products of these eukaryotic *OGG1* genes. The most typical domain is a helix–hairpin–helix (HhH) structural element followed by a glycine/proline-rich loop and a conserved aspartic acid (HhH-GPD motif), which has been identified in several different DNA glycosylases (14, 49). Conserved amino acid of lysine in the second helix and aspartic acid in the GPD motif, *e.g.*, Lys249 and Asp268 of human OGG1 protein, are important for the DNA glycosylase/AP lyase activity (49). Based on x-ray structural analysis of human OGG1 protein bound to a double-stranded oligonucleotide containing oh^{8}G (14), this domain is also important for the interaction with oh^{8}G or the

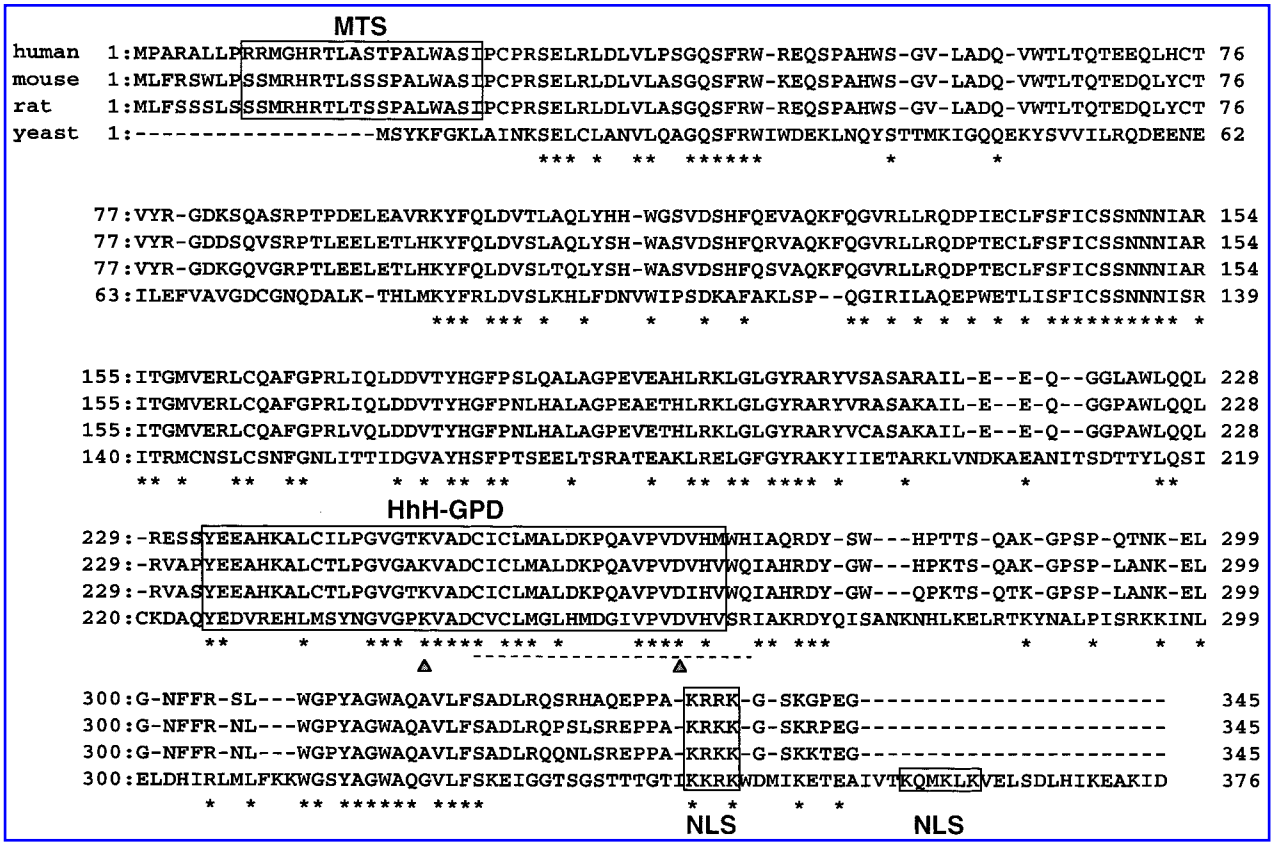

FIG. 3. Alignment of amino acid sequences of human, mouse, rat, and yeast OGG1 proteins. The amino acids identical in the four sequences are indicated by *. MTS, HhH-GPD, and NLS motifs are boxed. The catalytically important amino acids and a possible zinc finger motif are indicated by triangles and a dotted line, respectively.

DNA backbone phosphates near 8-hydroxydeoxyguanosine (oh^{8}dG). In detail, Gly245 and Val250 in the HhH-GPD motif, as well as Asn150 and His270 in other conserved domains, interact with the DNA backbone phosphates near oh^{8}dG, whereas Cys253 in this motif, as well as Gly42, Gln315, and Phe319 in other conserved domains, interacts with oh^{8}G extruded from the DNA helix (14). All amino acid residues described above and interacting with estranged cytosine opposite oh^{8}G in the complementary strand are located in the domain conserved among eukaryotic OGG1 proteins, including yeast protein. A possible C_2H_2 zinc finger domain (amino acid residues 253–273) is also present in the domain of HhH-GPD motif (3). When compared with the consensus primary and secondary structures of C_2H_2 zinc finger in animals (13, 37), some disagreements are seen between them (Fig. 4C). Thus, this C_2H_2 zinc finger motif of OGG1 protein would not be a typical one. Putative mitochondria targeting signals (MTS) are located in the amino-terminal end of mammalian proteins, whereas nuclear localization signals (NLS) are located near the carboxyl-terminal end of both yeast and mammalian proteins (1, 3, 9, 42, 48, 51, 55, 56, 58, 62, 67, 69, 72).

Expression of multiple OGG1 isoforms

The analyses of human OGG1 cDNA sequences have revealed that at least 13 OGG1 isoforms (types 1a–1h and types 2a–2e) are expressed in human cells by alternative splicing (1, 35, 51, 62). Type 1a is the originally cloned isoform (1, 3, 9, 42, 56). OGG1 isoforms are divided into two groups, type 1 and type 2, based on their carboxyl-terminal sequences. The type 1 isoforms utilize exon 7 as the last exon,

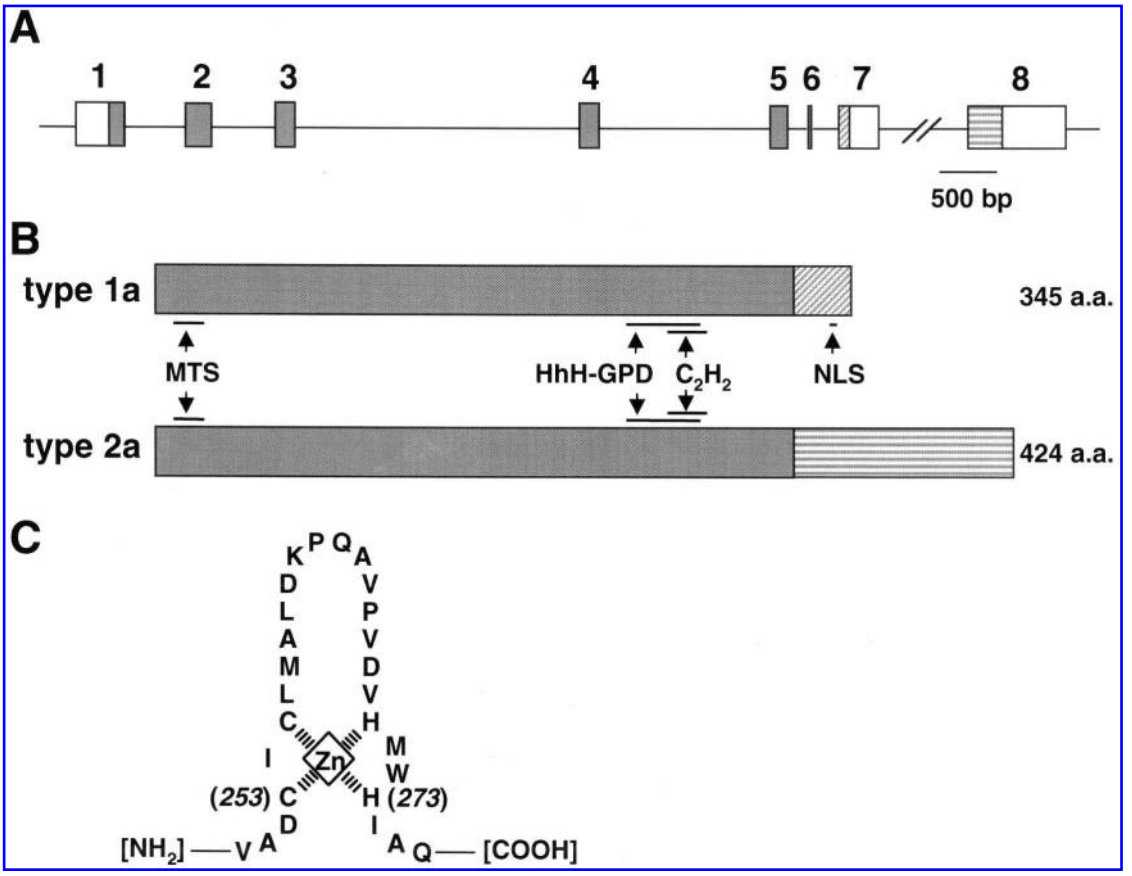

FIG. 4. Genomic structure of the human *OGG1* gene and schematic representation of OGG1 proteins. (**A**) Genomic structure of the *OGG1* gene. White rectangles represent untranslated regions of the OGG1 mRNA. (**B**) Structures of OGG1-types 1a and 2a proteins. (**C**) A schematic representation of a C_2H_2 zinc finger motif in the OGG1 protein. a.a., amino acids.

whereas the type 2 isoforms utilize exon 8, which is an additional alternative exon located downstream of exon 7 (Fig. 4A and B). In the level of mRNA expression, type 1a and type 2a are the most abundant among the type 1 and type 2 isoforms, respectively, in human cells (51, 62). In the level of protein expression, a 39-kDa protein corresponding to type 1a isoform is the most abundant in both cancerous and noncancerous human cells (28, 46, 62). Among the 13 isoforms, the entire HhH-GPD motif is retained in six types (type 1a–1c, 2a, 2d, and 2e) and all of them contained MTS. Therefore, the repair of mitochondrial DNA should be a function of these isoforms. It is noted that only the type 1a isoform retains both NLS and the entire HhH-GPD motif. MTS is also retained in the type 1a isoform, however, immunocytochemical studies revealed that the type 1a isoform mostly localizes in the nucleus (51, 62, 67). Therefore, type 1a is likely to be the most major protein for the repair of chromosomal DNA in the nucleus.

The 5′ upstream region of the *OGG1* gene lacks TATA-like sequence and comprises a high GC content, suggesting that the *OGG1* gene is a housekeeping gene (19, 30). The expression measured by the transcription from the promoter of the *OGG1* gene in cultured fibroblast cell lines does not vary during the cell cycle (19).

GENETIC ALTERATIONS OF THE *OGG1* GENE IN HUMAN CANCER

The human *OGG1* gene has been mapped to the short arm of chromosome 3, 3p26.2 (3, 42, 56, 57). As chromosome 3p is frequently deleted in various types of human cancers, including lung cancer and renal cell cancer (76, 77), it is of great interest to know whether the *OGG1* gene is inactivated in human cancer cells by two mutational events as in the case of typical tumor suppressor genes.

Recent studies have indeed shown the high frequency of loss of heterozygosity (LOH) at the *OGG1* gene locus in several types of human cancers (Table 1) (6, 10, 35, 73). If it is inactivated in cancer cells, genomic instability of cancer cells can be explained in part by the loss of OGG1 activities. However, overall frequencies of *OGG1* gene mutations are very low in several types of human cancers, including carcinomas of the lung, kidney, stomach, colorectum, and head and neck (Table 1) (6, 10, 16, 35, 36, 61). Therefore, the *OGG1* gene is not likely to be a major target gene on chromosome 3p that is inactivated by chromosomal losses and/or intragenic mutations in cancer cells.

All the mutations so far detected in cancer cells are missense point mutations resulting in the production of OGG1 proteins with amino acid substitutions (Table 2) (6, 7, 16, 29, 35, 61). Functional assays have been performed in some of those mutations by using base excision assay, DNA cleavage assay, and a complementation assay in *E. coli*. The results indicate that DNA repair activity is indeed reduced in some mutated OGG1 proteins. Repair activities of OGG1-Q46, Q131, and H154 proteins are lower than that of the wild-type OGG1 protein (6, 7, 14, 16, 35, 61). With regard to an R154 to H154 amino acid conversion found in a gastric cancer cell line, MKN1 (61), another potentially

Table 1. Frequency of *OGG1* Mutations and LOH at the *OGG1* Gene Locus in Human Cancer

		Frequency		
Organ	*Type*	*Mutation*	*LOH*	*Reference*
Lung	Cell line	0/52		35
Lung	Primary tumor	0/45	62%	35
Lung	Primary tumor	1/25		16
Stomach	Cell line	1/9		61
Stomach	Primary tumor	0/35		61
Kidney	Primary tumor	1/15		16
Kidney	Primary tumor	4/99	85%	6
Head and neck	Primary tumor	0/33	57%	10
Colorectum	Primary tumor	0/25		36

TABLE 2. TYPES OF *OGG1* MUTATIONS IN HUMAN CANCER

Mutated in	*Exon (codon)*	*Nucleotide*	*Amino acid*	*Functional assay*[a]	*Reference*
Primary renal cell cancer	1 (12)	G → A	G → E	G12•E12[b]	6
Primary renal cell cancer	1 (46)	G → A	R → Q	R46>Q46[c]	6, 7, 35
Primary lung cancer	3 (131)	G → A	R → Q	R131>Q131	16
Gastric cancer cell line, MKN1	3 (154)	G → A	R → H	R154>H154[d]	7, 14, 61
Primary renal cell cancer	3 (169)	G → A	R → Q	R169•Q169[b]	6
Leukemic cell line, KG-1	4 (229)	G → A	R → Q	U937>KG-1[d]	29
Primary renal cell cancer	4 (232)	T → A	S → T	S232•T232[b]	6, 16

[a]A•B indicates that A has almost the same activity as B, whereas A>B indicates that A has greater activity than B.
[b]Based on DNA cleavage assay.
[c]Based on base excision assay, DNA cleavage assay, and complementation assay in *E. coli.*
[d]Based on base excision assay and DNA cleavage assay.

dangerous feature was reported. OGG1-H154 protein exhibited a substantial increase in the activity to excise oh^{8}G paired with bases other than cytosine, particularly adenine (7, 14); therefore, this mutant appears to be promutagenic. The finding that R154 is one of the residues interacting with the base opposite oh^{8}G (14) probably indicates the alteration of substrate specificity. In addition to these three mutations, OGG1-Q229 protein was also suggested to have a lower repair activity than the wild-type protein, because a leukemic cell line, KG-1, which showed a homozygous mutation resulting in the production of OGG1-Q229, had extremely low oh^{8}G repair activity (29).

GENETIC POLYMORPHISMS OF THE OGG1 GENE IN ASSOCIATION WITH REPAIR ACTIVITIES OF THE GENE PRODUCT

It is also important to know whether repair activities of OGG1 protein are different among individuals, because such a difference could be associated with cancer susceptibility and aging in each individual. For this reason, we and others have extensively searched for genetic polymorphisms in the human *OGG1* gene in association with repair activities of the protein. Up to the present, various types of genetic polymorphisms have been identified in the human *OGG1* gene locus (Table 3) (6, 7, 10, 16, 20, 31, 35, 36, 61, 73).

TABLE 3. GENETIC POLYMORPHISMS IN THE *OGG1* GENE LOCUS

Location	*Nucleotide*	*Amino acid*	*Functional assay*[a]	*Reference*
Exon 1 (−23 bp from the initiation codon)	A/G			31, 35
Exon 1 (−18 bp from the initiation codon)	G/T			31, 35, 36
Exon 1	G/A	R46Q	R46>Q46[b]	6, 7, 35, 73
Exon 2	G/T	A85S	A85•S85[c]	6, 16
Exon 2	G/A	K98K		35, 36
Exon 4	C/T	G220G		6
Intron 4 (IVS4-15)	C/G			10, 35
Exon 6	G/A	G308E	G308•E308[d]	6, 10
Exon 7	G/A	L323L		6
Exon 7	C/G	S326C	S326>C326[e]	7, 20, 35, 61

[a]A•B indicates that A has almost the same activity as B, whereas A>B indicates that A has greater activity than B.
[b]Based on base excision assay, DNA cleavage assay, and complementation assay in *E. coli.*
[c]Based on DNA cleavage assay.
[d]Based on DNA cleavage assay and complementation assay in *E. coli.*
[e]Based on base excision assay and complementation assay in *E. coli.*

As a genetic polymorphism associated with an exchange of amino acid, there is a C/G polymorphism resulting in the production of OGG1-Ser326 and -Cys326 proteins. The activity in the repair of oh^{8}G is greater in OGG1-Ser326 protein than in OGG1-Cys326 protein in the complementation assay of an *E. coli mutM mutY* strain (35). In addition, the catalytic efficiency (k_{cat}/K_m) of excision for oh^{8}G from γ-irradiated DNA by OGG1-Ser326 protein is twice as great as that by OGG1-Cys326 protein (7, 20). We therefore examined allele distributions of the Ser326Cys polymorphism in a case-control study of male lung cancer in Okinawa (66). In a comparison of the Cys/Cys genotype with Ser/Cys and Ser/Ser genotypes combined, the increased risk was observed in squamous cell carcinoma and nonadenocarcinoma after adjusting for age and smoking history, and the odds ratios were 3.01 and 2.18, respectively. Thus, it was indicated that the individuals with the Cys/Cys genotype are more susceptible to squamous cell lung carcinoma than those with the Ser/Cys and Ser/Ser genotypes. However, in a Caucasian population, this Ser326Cys polymorphism does not seem to be associated with lung cancer (73).

A G/A genetic polymorphism in exon 1 is associated with the production of OGG1-Arg46 and -Gln46 proteins (35, 73). Repair activities of OGG1-Gln46 protein are lower than those of OGG1-Arg46 protein (7, 35). Moreover, the A type in this position, which is rare in the human population (35, 73), causes alternative splicing of the human *OGG1* gene (35). Due to a partial inactivation of the 5′ splice site in intron 1, a readthrough transcript of intron 1 encoding a truncated OGG1 protein is expressed. In fact, in a lung cancer cell line, NCI-H526, which exhibits the homozygous A type polymorphism in this position, the amount of 39-kDa protein corresponding to the OGG1-type 1a isoform was extremely low (62). Interestingly, this A type polymorphism was also detected as a somatic change in a primary clear cell carcinoma of the kidney (7).

To date, little is known about whether, or how, genetic polymorphisms of other oh^{8}G repair genes affect DNA repair function. Recently, some variant types of APEX protein were reported to have reduced 5′ AP endonuclease activities (26). Although 3′-phosphodiesterase activities of these variants were not examined in their studies, the reductions in the activities of these variant types compared with the wild type are expected. Thus, differences in the total oh^{8}G repair activities in human cells, due to the combination of genetic polymorphisms in the *OGG1* and *APEX* genes, could be critical for defining the mutation rate induced by oh^{8}G. In addition, genetic polymorphisms in the *MYH* base excision repair gene, transcription-coupled repair genes, and mismatch repair genes may also be involved in the total oh^{8}G repair activity in cells. Furthermore, as there are various carcinogens that generate reactive oxygen species, the combination of genetic polymorphisms between oh^{8}G repair genes and genes involved in the detoxification of such carcinogens may contribute to defining cancer susceptibility in each individual.

ACKNOWLEDGMENTS

We regret that all relevant articles could not be cited due to space constraints. Work in our laboratory was supported in part by Grants-in-Aid from the Ministry of Health, Labor and Welfare for the 2nd-Term Comprehensive 10-Year Strategy for Cancer Control and from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

ABBREVIATIONS

AP, apurinic/apyrimidinic; HhH, helix–hairpin–helix; LOH, loss of heterozygosity; MTS, mitochondria targeting signal; NLS, nuclear localization signal; oh^{8}dG, 8-hydroxydeoxyguanosine; oh^{8}G, 8-hydroxyguanine; SAM, senescence-accelerated mouse.

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Received for publication December 3, 2000; accepted January 16, 2001.

This article has been cited by:

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