8-Oxoguanine (G*), induced by reactive oxygen species, is mutagenic because it mispairs with A. The major G*-DNA glycosylase (OGG), namely, OGG1 in eukaryotes, or MutM in *Escherichia coli*, excises G* when paired in DNA with C, G, and T, but not A, presumably because removal of G* from a G*-A pair would be mutagenic. However, repair of G* will prevent mutation when it is incorporated in the nascent strand opposite A. This could be carried out by a second OGG, OGG2, identified in yeast and human cells. We have characterized a new OGG activity in *E. coli* and then identified it to be endonuclease VIII (Nei), discovered as a damaged pyrimidine-specific DNA glycosylase. Nei shares sequence homology and reaction mechanism with MutM and is similar to human OGG2 in being able to excise G* when paired with A (or G). Kinetic analysis of wild type Nei showed that it has significant activity for excising G* relative to dihydrouracil. The presence of OGG2 type enzyme in both *E. coli* and eukaryotes, which is at least as efficient in excising G* from a G*-A (or G) pair as from a G*-C pair, supports the possibility of G* repair in the nascent DNA strand.

8-Oxoguanine (8-oxoG or G*), formed by reactive oxygen species in cellular DNA and in the deoxynucleotide pool (1, 2), may be the most critical mutagenic base because of its propensity for mispairing with A during DNA replication (2, 3). Furthermore, reactive oxygen species, which are formed both endogenously as by-products of respiration and during the inflammatory response, are the most pervasive cellular genotoxic agents (4, 5). Reactive oxygen species-induced mutations have been implicated in the etiology of a wide variety of diseases including cancer and arthritis and in aging (6, 7). In all organisms tested so far from *Escherichia coli* to mammals, 8-oxoG in DNA is repaired primarily via the DNA base excision repair pathway, and repair is initiated by the action of 8-oxoguanine-DNA glycosylase (OGG) (8–10). This DNA glycosylase/AP lyase excises the base lesion by breaking the glycosylic bond via formation of a covalent Schiff base with the amino group of Pro for the *E. coli* enzyme or the ε-NH₂ group of an internal Lys for the eukaryotic enzymes. This results in cleavage of the DNA phosphodiester backbone because of β (or ββ) elimination (8–11). The transient covalent intermediate forms a stable product after its reduction by NaBH₄ or NaCNBH₃ and is called the “trapped complex” (8–11). The cleaved terminus upstream of the G* site contains a 3’-phospho-α, β-unsaturated aldehyde or 3’-phosphate resulting from the β or ββ reaction, respectively. Subsequent steps in repair involve removal of the 3’-blocking groups followed by DNA gap filling and ligation of the broken ends (12).

The major OGG (OGG1) in yeast and mammals corresponds to the only one identified in *E. coli*, which was named MutM or formamidopyrimidine-DNA glycosylase (the product of the *mutM*/*pgp* gene) in their substrate specificity. All of these enzymes were shown to excise G* from G*-C, G*-G, or G*-T pairs in duplex DNA but not from a G*-A pair. This observation, first made in *E. coli*, led to the postulation of the “GO system” (13–15). In this model, G* formed directly or after incorporation in DNA opposite C is repaired by MutM. However, unrepaired G* could pair with A during DNA replication. In such an event, MutY, a G* (G)-specific adenine-DNA glycosylase (8, 14), removes the A residue and thus provides a second chance for restoring the original DNA sequence by removing G* in a subsequent step when a G*-C pair is formed after repair. It is obvious that mutation will result if G* from a G*-A pair is removed by MutM (14, 15).

However, mutagenesis due to 8-oxoguanine is rather complex, because 8-oxoG is not only generated in DNA in *situ* but may also be incorporated into DNA from reactive oxygen species-induced 8-oxo-dGTP in the nucleotide pool (2). MutT, ubiquitous 8-oxo-dGTPase, prevents incorporation of 8-oxoG by degrading the triphosphate (2). The fact that the spontaneous mutation frequency of the *mutT E. coli* mutant is much higher than that of the *mutT* mutant (2) indicates that a significant potential for mutation because of 8-oxoG incorporation opposite A exists during DNA replication. Furthermore, removal of A by MutY in such a situation where 8-oxoG is incorporated in the nascent strand opposite A will fix rather than prevent mutation. This paradox suggests the need for differential removal of 8-oxoG when incorporated into DNA versus being generated in...
90 mM Tris-Borate (pH 8.3), and 2 mM EDTA. The radioactivity in the supernatant with 35–55% saturation of ammonium sulfate, the precipitation, the 15-mer cleaved product was separated by electrophoresis in a 20% denaturing polyacrylamide gel containing 7 M urea, 90 mM Tris-Borate (pH 8.3), and 2 mM EDTA. The radioactivity in the gel was quantitated by analysis in a PhosphorImager (Molecular Dynamics).

Purification of a Novel 8-OxoG-DNA Glycosylase Activity from mutM E. coli—E. coli BH20 (mutM::kan) and BW35 (nei::Cm) were generously provided by Drs. K. Tanou and S. S. Wallace, respectively. E. coli DE884 (mutM::kan nei::Cm) was constructed by P1 transduction using BH20 and BW35 as recipient and donor strains for the nei::Cm allele, respectively. The T7 RNA polymerase gene was introduced in DE884 by using the lysogenization kit (Novagen) according to the manufacturer’s protocol (17).

Preparation of Substrate DNA—All of the studies described here except in Fig. 6 involved a 31-mer oligonucleotide (Fig. 1, Seq. A) containing a single G* at position 16, which was characterized by mass spectroscopic analysis and purchased from Midland Certified Corp. (Midland, TX). Some subsequent studies were also carried out with a 43-mer (Operon Technologies) and another 31-mer G*-containing oligonucleotide (Midland Certified Corp.) of a different sequence as shown in Fig. 1. Oligos complementary to the G*-containing oligonucleotides were synthesized by the Recombinant DNA Laboratory at UTMB, and all oligos were gel-purified before use.

Assay of Lesion-specific DNA Strand Incision—Because only the β elimination product and no free AP site was detected during Nei reaction, as shown under “Results,” the DNA glycosylase activity of Nei was routinely measured by the strand incision assay. This assay was carried out at 37 °C for 30 min in a 50-μl reaction mixture containing 20 fmol of 32P-labeled substrate DNA, crude extract (10 μg) or purified enzyme (amount as described in the figure legends) in a buffer containing 25 mM Tris-HCl (pH 7.5), 2.5 mM EDTA, 1 mM DTT, 5% glycerol, and 50 mM NaCl as described earlier (9). After termination of the reaction by extraction of the mixture with phenol/chloroform, followed by ethanol precipitation, the 15-mer cleaved product was separated by electrophoresis in a 20% denaturing polyacrylamide gel containing 7 M urea, 90 mM Tris-Borate (pH 8.3), and 2 mM EDTA. The radioactivity in the gel was quantitated by analysis in a PhosphorImager (Molecular Dynamics).

Purification of Recombinant Nei from mutM E. coli—E. coli HB101 containing the nei expression plasmid cloned into pET22b vector was a gift from Dr. Z. Hatahet (18). The plasmid was extracted, and the wild type of the nei gene was confirmed by sequencing the coding region. E. coli DE884 (DE3) was transformed with the nei expression plasmid and then grown at 37 °C in 1 liter of L broth containing 5 μM ZnCl2 and 100 μg/ml ampicillin. At A590 of 0.5, isopropyl-1-thio-β-D-galactopyranoside was added to 100 μM, and the culture was grown at 30 °C for 12 h. The cells were then pelleted by low speed centrifugation and sonicated in a buffer containing 50 mM Tris-HCl, pH 7.5, 400 mM NaCl, 1 mM EDTA, and 0.1 mM DTT. The sonicated extract was loaded onto DEAE-cellulose (Amersham Pharmacia Biotech). After extensive washing with buffer A containing 100 mM NaCl, the purified protein was eluted at 0.25–0.3 M NaCl. Active fractions were then pooled and concentrated by Amicon and then onto a 120-ml Superdex-75 equilibrated with buffer A containing 150 mM NaCl. Active fractions were quickly frozen in liquid nitrogen and stored in −80 °C for future studies.

Kinetics of Nei Reaction with 8-OxoG- and DHU-containing Duplex Oligonucleotide Substrate—One pmol Nei was incubated at 37 °C with 8-OxoG (31-mer, 20–100 mM) or DHU (5–20 mM) containing duplex oligonucleotide substrate for 10 and 5 min, respectively. We confirmed that the enzyme maintains linear kinetics for at least up to 20 min. The reaction buffer (20 μl) contained 20 mM Tris-HCl, pH 7.5, 50 mM NaCl, 0.1 mM DTT, 1 mM EDTA, 100 μg/ml bovine serum albumin, and 25–30 fmol of 32P-labeled substrate. The reaction was stopped by adding 10 μl of formamide/dye containing 10 mM NaOH and was resolved on a 20% polyacrylamide-urea gel. The radioactivity in the bands of the gel was quantitated with a PhosphorImager (Molecular Dynamics), and the data were fitted to the Michaelis-Menten equation by using data analysis/graphics application program of KaleidaGraph.

Assay of 8-OxoG Release from 8-OxoG-containing DNA—One hundred pmol of 8-oxoguanine-containing substrate DNA was incubated with 30–35 pmol of Nei or MutM for 4 h at 37 °C. The reaction buffer contained 30 mM Tris-HCl, pH 7.5, 1 mM EDTA, 0.1 mM DTT, 100 mM KCl, and 5 μg of bovine serum albumin in a 100-μl reaction volume. As control, DNA substrates were incubated with inactivated enzyme or without the enzyme, and all the reactions were performed in duplicate. Inactivation of the enzyme was achieved by heating at 100 °C for 15 min, and the DNA samples were precipitated with 270 μl of ethanol. DNA pellets and supernatant fractions were separated. Supernatant fractions were freed from ethanol under vacuum in a SpeedVac and subsequently lyophilized for 18 h. Lyophilized fractions were derivatized and then analyzed by gas chromatography/isotope-dilution mass
The Discovery of a Second 8-OxoG-DNA Glycosylase Activity in E. coli—The discovery of a second OGG, OGG2, in yeast and human cells (9, 16) raised the possibility of the presence of a similar enzyme in bacteria including E. coli in which only one 8-oxoG-DNA glycosylase, namely, MutM, was identified so far. Ten μg of crude extracts from wild type and mutM E. coli were incubated with 5'-labeled duplex oligos containing G* paired with G, C, and A, and the products were analyzed in a 20% denaturing polyacrylamide gel. The cleavage of G*-A oligo in the G* strand (Fig. 2A, lane 4) by extract of wild type E. coli suggested the presence of a second OGG in wild type E. coli, because MutM, the only known OGG, does not cleave this substrate (13). This possibility was further supported by the presence of OGG activity in the mutM E. coli extract (lanes 5–7); the oligos with G*-G and G*-A pairs were the preferred substrates for this enzyme (lanes 6 and 7). Because MutM does not remove G* from a G*-A pair (13), similar levels of activity were observed in extracts of the wild type and mutM E. coli for the oligo with the G*-A pair (lanes 4 and 7). We confirmed that the strand incision activity in E. coli extract was specific for the G*-containing strand because a control oligo, identical to the G* oligo except for substitution of G* with G, was not cleaved by the extract. At the same time, no cleavage of the complementary strand was observed when the strand containing the 32P label was used as the substrate (data not shown). Furthermore, the lack of detectable cleavage of the labeled G* strand in the G*-G duplex oligo by an excess human AP endonuclease or E. coli endonuclease IV indicated the lack of contamination of the G* oligo with an AP site (data not shown).

We then examined the nature of the 3’ terminus of the cleaved product using a partially purified protein from mutM E. coli. Fig. 2B shows that the upstream fragment contained 3’-phosphate (lane 3), which was identical to the β-elimination product of MutM reaction with the same substrate (lane 2; 21). These results indicate that the second G*-removing enzyme in E. coli, like MutM, is an 8-oxoguanine DNA glycosylase/AP lyase and carries out βδ elimination.

Identification of Endonuclease VIII (Nei) as the Second 8-OxoG-DNA Glycosylase—We extensively purified 8-oxoG-DNA glycosylase activity from mutM E. coli extract by assaying the cleaved product or the trapped complex. The ability of OGG to form a trapped complex with 32P-labeled substrate DNA helped us to identify the specific enzyme band. The trapped complex was purified by binding to streptavidin-containing beads, and the eluted proteins were separated by SDS-polyacrylamide gel electrophoresis and then transferred to a polyvinylidene difluoride membrane. Coomassie Blue staining of the membrane showed the presence of four to five major bands (Fig. 3A), only one of which was radiolabeled (Fig. 3B). Our initial attempt to determine the N-terminal peptide sequence failed suggesting that the N terminus of the intact protein may be blocked. We then digested the eluted radioactive band with endo Lys C, and the peptides were separated by capillary high pressure liquid chromatography for sequencing. The sequence analysis of two purified peptides were GKPLTDV and TTLSS-RPF. These sequences are identical to the sequences of Nei from amino acid residues 20–26 and 248–255, respectively.

8-OxoG-DNA Glycosylase Activity of Nei—We then purified Nei from mutM nei E. coli harboring the expression plasmid for Nei to apparent homogeneity (Fig. 4) and tested the enzyme for 8-oxoG-DNA glycosylase activity. Nei had OGG activity, although, the DHU-A repair activity is significantly higher than G* repair (Fig. 5). Of the three G* base pairs, the G*-G pair was the preferred substrate for Nei. Nei, unlike MutM, could remove G* from the G*-A pair as well (Fig. 5, lane 3).

In view of the possibility that the Nei activity on G*-A pair may be affected by the sequence context of the 8-oxoG in the substrate oligos used, we tested G*-A specific DNA glycosylase/AP lyase activity of several duplex oligos of different sequences and size. Fig. 6 shows that with the same concentration of substrate and enzyme as used in the experiment described in Fig. 5, there was a significant difference in the amount of the cleavage product. In fact, the best substrate was the 43-mer oligo, which was not routinely used in this study. We also observed robust OGG activity with a 54-mer 8-oxoG duplex oligo of an entirely different sequence (data not shown).

Release of 8-OxoG from Duplex Oligo Substrate by Nei—To confirm that Nei is indeed an 8-oxoG-DNA glycosylase that releases 8-oxoG, we tested for the free base in the reaction mixture. After incubation of Nei with G*-G-containing oligonucleotide, purified Nei released a product that had the same retention time as the authentic G* as analyzed by gas chromatography/mass spectrometry. Forty-five pmol of G* was released from 100 pmol of substrate by 33 pmol of Nei (Table I),
whereas in a duplicate, independent reaction about 50 pmol of strand incision product was generated (data not shown). In this experiment, MutM was used as a positive control, which is also active toward the G∗G-containing substrate. Furthermore, we made similar observations about the release of 8-oxoG from G∗A and G∗C-containing substrates (data not shown). We examined whether Nei excised 8-oxoG without further cleavage of the resulting AP site. However, lack of additional strand incision of the G∗G substrate oligo with *E. coli* endonuclease IV, an AP endonuclease, after Nei treatment indicated a concerted action of Nei in base release and βγ elimination (data not shown).

**Kinetic Properties of Nei**—Kinetic properties of Nei using DHU:A and G∗N substrates were compared (Table II). This protein released DHU and G∗ in a dose- and time-dependent manner. The active enzyme concentration was determined to be 60%, as described previously (22). Km and kcat determination were carried out in the linear range of enzyme activity. The Km for the G∗-substrates was almost 4–5-fold higher than for the DHU substrate. Furthermore, Nei was catalytically more efficient in releasing DHU than G∗ from substrates with identical sequence context.

**DISCUSSION**

Our discovery of a second 8-oxoG-DNA glycosylase activity in human cell extracts, which is antigenically distinct from the cloned OGG1, and which, unlike OGG1, preferentially excises 8-oxoguanine from DNA when paired with G and A, led us to propose a distinct role of this new enzyme, named OGG2, in excising G∗ from the nascent strand (9). Recent studies showing that mouse cells lacking OGG1 are competent in slow but significant removal of 8-oxoG from DNA particularly in proliferating cells support the presence of a second OGG in mammalian cells (23, 24). This was further supported by the observation that transcription coupled repair of 8-oxoG was not significantly affected by inactivation of OGG12 and is presumably carried out by the second OGG in mouse cells. A similar OGG2 activity was discovered earlier in yeast (16, 25). To
establish that the dual mode of 8-oxoG repair exists in all organisms, we needed to show that an OGG2 type enzyme, which is distinct from MutM/formamidopyrimidine-DNA glycosylase, also exists in bacteria such as E. coli. The apparent lack of earlier efforts to examine the presence of other G*-specific DNA glycosylase in mutM E. coli is surprising. In any event, we tested extracts of mutM E. coli and easily identified significant activity of an uncharacterized G*-specific DNA glycosylase/AP lyase. Because an AP lyase forms a trapped complex with the substrate in the presence of NaCNBH₃, we purified the biotinylated trapped complex coupled to streptavidin-magnetic beads and then sequenced an internal peptide. De novo identification of this activity as Nei provided the initial evidence for the intrinsic OGG activity of this enzyme. Measurement of release of 8-oxoG in the reaction product of purified Nei confirmed its identity as an 8-oxoG-DNA glycosylase. More importantly, when the G*-A containing substrate was used, the OGG activity was mostly contributed by Nei because MutM is inactive with this substrate (Fig. 2, lanes 4 and 7). To provide genetic evidence for the Ogg activity of Nei, the nei gene was inactivated in mutM E. coli. It is interesting that a small amount of OGG type activity persisted even in the mutM nei E. coli (Fig. 7, lanes 5–7). The specific activity of the mutM E. coli extract was about 1 pmol of substrate (G*-G-containing oligo) cleavage/mg of protein/min at 37 °C compared with 0.25 pmol of substrate cleavage/mg of protein/min of the mutM nei E. coli extract. Thus Nei contributed about 70% of the OGG type activity. We were unsuccessful in purifying and thereby identifying this second, minor enzyme.

Nei was identified earlier as the second DNA glycosylase, after Nth, specific for oxidized pyrimidines, e.g. thymine glycol and 5-hydroxycytosine, and also DHU (26–28). The substrate preferences of Nei and Nth are overlapping but not identical (26).

Despite similar substrate preference, Nth and Nei have no sequence homology, nor similar functional motifs (26, 27). For example, Nth is the prototype of the class of DNA glycosylase whose substrate binding is mediated by "helix-hairpin-helix" motif and which contains a [4Fe-4S] cluster also needed for DNA binding (29, 30). Nei, on the other hand, has extensive sequence homology with MutM. The N-terminal Pro of MutM was identified to be the active site nucleophile of this enzyme (31). Because the N-terminal Pro and five of the first six residues are identical in Nei and MutM, it is expected that the N-terminal Pro is also the active site nucleophile in Nei, which is covalently linked to the deoxyribose in the trapped complex (26). The fact that we could not determine the N-terminal peptide sequence of the Nei trapped complex, as was the case for MutM (31), supports this possibility. Furthermore, Nei behaves like MutM in carrying out ββ elimination and generating a 3'-phosphate terminus in the cleaved DNA oligo after excision of 8-oxoguanine. Nth, on the other hand, generates β elimination products (22).

Based on the similarities between MutM and Nei, it was not completely surprising that Nei possesses 8-oxoG excision activity. Conversely, several recent studies have shown that MutM could also excise oxidized pyrimidines such as uracil glycol, 5-hydroxyuracil, or 5-hydroxycytosine (18, 32). Thus MutM and Nei may have a significant overlap in their substrate specificity. What is surprising, however, is the preference of Nei for G* when paired with purines and its relatively weak activity with the G*-C pair, the preferred substrate of MutM and eukaryotic OGG1 (9, 33–35). While our manuscript was in preparation, Blaisdell et al. (36) published a paper in which they showed that Nei had weak OGG activity with a G*-C-containing duplex oligo, but no significant activity was observed with the G*-A pair-containing substrate. We are unable to explain the discrepancy between their results and ours. It is possible that the sequence context of the oligo substrate used in their study inhibited 8-oxoG excision by Nei. In fact, we have shown (Fig. 6) that the specific OGG activity of Nei varied 4–5-fold with the sequence context of the G*-A pair in the oligos we tested. In any case, we decided to eliminate a remote possibility that the nei gene was mutated somehow in our E. coli strain, which caused its altered substrate specificity. So we cloned the nei gene, including its own promoter from mutM E. coli by PCR and confirmed the presence of wild type sequence in the clone by matching with the E. coli GenBank™ data base and then confirmed G*-A-specific G* excision activity of the expressed protein (data not shown).

Using 31-mer oligonucleotide duplexes of identical sequence (Seq A) except for the presence of DHU or G* at position 16, we compared the kinetic parameters of Nei for various G* pairs and a DHU-A pair. It is evident that DHU was a better substrate for Nei than 8-oxoG, in regard to substrate affinity as judged by the Kᵣ values (Table II). However, the enzyme turnover for G* excision activity from a G*-A or G*-G pair was only 5–7-fold less than for DHU excision activity and thus should be physiologically significant. More importantly, the order of substrate preference for G*-G>G*-A>G*-C as observed with E. coli extract was the same as with the pure Nei protein. Recently two distinct OGGs from the bacterium Deinococcus radiodurans have been characterized, one of which was active toward thymine glycol and appears to be a homolog of Nei (37).

It is somewhat puzzling that both human OGG2 and E. coli Nei prefer the G*-G pair to G*-A and other G* base pairs. However, it was shown earlier that G* can pair with G as a 6-eneolate-8-keto tautomer (38). Furthermore, MutY was shown to excise not only A but also G when paired with 8-oxoG (39). Therefore, it is possible that the G*-G pair could occur in vivo and is subject to repair by OGG2 or Nei. It is interesting to note in this context that yeast OGG2 was found to be identical to Ntg1, an oxidized pyrimidine-specific DNA glycosylase, which is similar to the Ntg2, the other glycosylase with a similar
substrate range (16, 20). Whereas both Ntgs belong to the Nth family in regard to structural motifs, only Ntg1 has OGG2 type activity. This activity, as was found to be the case for Nei, appears to be weaker than its oxidized pyrimidine-specific DNA glycosylase activity.

Taken together, our results support the prediction that OGG2 type activity, which excises G* from a G*zA pair, is ubiquitous and that it may have an important role in 8-oxoG repair in proliferating cells and in transcriptionally active genes.

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Characterization of a Novel 8-Oxoguanine-DNA Glycosylase Activity in *Escherichia coli* and Identification of the Enzyme as Endonuclease VIII

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