Recognition of Formamidopyrimidine by Escherichia coli and Mammalian Thymine Glycol Glycosylases

DISTINCTIVE PAIRED BASE EFFECTS AND BIOLOGICAL AND MECHANISTIC IMPLICATIONS*

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The activity of prokaryotic and mammalian thymine glycol (Tg) glycosylases including Escherichia coli endonuclease III (Endo III) and endonuclease VIII (Endo VIII) and mouse Endo III homologue (mNth1) for formamidopyrimidine (Fapy) has been investigated using defined oligonucleotide substrates. 2,6-Diamino-4-hydroxy-5-N-methylformamidopyrimidine, a methylated Fapy derived from guanine, was site specifically incorporated in the oligonucleotide. The substrates containing Fapy:N pairs (N = A, G, C, T) as well as a Tg:A pair, a physiological substrate of Endo III, Endo VIII, and mNth1, were treated by the enzymes and nicked products were quantified by gel electrophoresis. The activity of Endo III and Endo VIII for Fapy varied markedly depending on the paired base, being the highest with G (activity relative to Tg = 0.55 (Endo III) and 0.41 (Endo VIII)) and the lowest with C (0.05 (Endo III) and 0.06 (Endo VIII)). In contrast, mNth1 recognized all Fapy pairs equally well and the activity was comparable to Tg. The results obtained in the nicking assay were further substantiated by the analysis of the Schiff base intermediate using NaBH₄ trapping assays. These results indicate that Escherichia coli and mammalian Tg glycosylases have a potential activity to recognize Fapy. However, as demonstrated for Fapy:C pairs, their distinctive activities implicate unequal participation in the repair of Fapy lesions in cells.

DNA damage caused by exogenous and endogenous agents is a major threat to genetic integrity of cells, and when unrepaired, it results in lethal and/or mutagenic events of cells (1). The deleterious effects of DNA damage have been also implicated in carcinogenesis and aging (2, 3). Among the diverse DNA lesions thus far identified, alterations of the base moiety caused by reactive oxygen species constitute one of the major classes of DNA damage. In cells, this class of damage is generally restored by the base excision repair (BER) pathway, a highly conserved mechanism across species (4, 5). The BER process for oxidized bases is initiated by DNA N-glycosylases that remove damaged bases from DNA. In Escherichia coli, DNA N-glycosylases responsible for this reaction are basically classified into two subgroups depending on the substrate, albeit some overlapping specificities. Oxidized pyrimidine bases such as thymine glycol (Tg) and 5-hydroxycytosine, etc., are excised from DNA by endonuclease III (Endo III) and endonuclease VIII (Endo VIII) (5, 6) encoded by the nth and nei genes, respectively (7–9). In contrast, oxidized purine bases such as 7,8-dihydro-8-oxoguanine (8-oxoG) and formamidopyrimidine (Fapy) are removed by formamidopyrimidine DNA glycosylase (Fpg) (10, 11) encoded by the fpg/mutM gene (12). The nth nei double mutant of E. coli lacking Endo III and Endo VIII exhibits a mutator phenotype and a increased sensitivity to hydrogen peroxide and ionizing radiation (8, 9). The mutations observed for the double mutant are mostly C → T transitions probably arising from impaired excision of oxidized cytosine lesions (13). The fpg mutant of E. coli deficient in Fpg shows a mutator phenotype though the sensitivity to ionizing radiation or hydrogen peroxide remains unchanged (14, 15). The frequent mutations observed for the fpg mutant are G → T transversions due to impaired excision of 8-oxoG (15). Thus, the substrate specificity of the two subgroups of DNA N-glycosylases correlates fairly well with the phenotype of their mutants.

Recently, functional homologues of Endo III (Ntg1 and Ntg2 proteins (also called Scr1 and Scr2)) and Fpg (yOgg1 protein) have been identified from Saccharomyces cerevisiae, and the substrate specificities of the expressed proteins have been studied. The yOgg1 protein recognizes 8-oxoG and Fapy, showing a substrate specificity similar to Fpg (16, 17). Ntg1 and Ntg2 proteins recognize a variety of oxidized pyrimidines, such as Tg and 5-hydroxycytosine, that are also substrates for Endo III (18–23). Despite such similar substrate specificities between Endo III and its S. cerevisiae homologues, the latter enzymes also recognize Fapy derivatives (18–20, 22) that have been reported not to be excised by Endo III (6) and its human homologue (hNTH1) (24). The additional substrate specificity of Ntg1 and Ntg2 for Fapy derivatives is rather unexpected since both proteins show significant amino acid sequence homology to Endo III (24% identity and 46% similarity (Ntg1), 24% identity and 41% similarity (Ntg2)) encoded by the nth neoI and nth nei genes, respectively. Although the Ntg1 and Ntg2 proteins are not related to the Endo III homologues, they are functionally similar to Fpg, showing similar rates of excision of selected lesions. These data demonstrate that these enzymes are involved in a BER pathway for Fapy and 8-oxoG.
25% identity and 51% similarity (Ntg2). Moreover, the enzymes have the helix-hairpin-helix (HhH) motif and key amino acids (Lys-243 and Asp-262 (Ntg1), Lys-248 and Asp-267 (Ntg2)) possibly involved in DNA recognition and catalysis. The HhH motif and catalytic amino acids are highly conserved in Endo III homologues (25). Ntg2 (but not Ntg1) also possesses a conserved 4Fe-4S cluster near the C terminus.

The apparently different activities toward a Fapy substrate of Endo III and its S. cerevisiae homologues (Ntg1 and Ntg2) raised a question whether the activity is peculiar to Ntg1 and Ntg2 or has been somehow overlooked in previous studies on the Endo III homologues from other sources. In view of the question above, we have reinvestigated the activity of prokaryotic and mammalian thymine glycol glycosylases for Fapy using defined oligonucleotide substrates. We report here that thymine glycol glycosylases including Endo III, Endo VIII, and the mouse Endo III homologue (mNth1/mNthl1) have a potential activity to excise Fapy from DNA. However, the activity of Endo III and Endo VIII varies dramatically depending on the base opposite Fapy, whereas the activity of mNth1 is essentially independent of the paired base and is comparable to that for Tg.

**EXPERIMENTAL PROCEDURES**

**Enzymes**—*E. coli* DNA polymerase I Klown fragment and T4 polynucleotide kinase were purchased from Life Technologies, Inc. and New England Biolabs, respectively. Endo III, Endo VIII, and Fpg proteins were overexpressed in *E. coli* cells harboring plasmids containing the *nth*, *nei*, or *fpj* gene (gifts from S. S. Wallace and Z. Hatahet) and purified as described (8, 26). Expression and purification of the mouse Endo III homologue (mNth1/mNthl1) have been reported previously (27). Human 7,8-dihydro-8-oxoguanine glycosylase (hOGG1/hMMH, type 1a isoform) was generously supplied by Nishimura (28). The repair enzymes used in this study were apparently homogenous in SDS-PAGE analysis.

**Oligonucleotides**—Oligonucleotides used in this study are listed in Table I. The oligonucleotides except 25FP and 19TG were synthesized by the phosphoramidite method and purified by reversed phase HPLC. 25FP containing a single 2,6-diamino-4-hydroxy-5-N-methylformamidopyrimidine (Fapy), O = 7,8-dihydro-8-oxoguanine (8-oxoG), Y = cis-thymine glycol (Tg).

25FP containing a single 2,6-diamino-4-hydroxy-5-N-methylformamidopyrimidine (Fapy), O = 7,8-dihydro-8-oxoguanine (8-o xoG), Y = cis-thymine glycol (Tg).

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**RESULTS**

**Activity of Endo III, Endo VIII, and mNth1 for Fapy Paired with C**—To examine the incision activity for Fapy, Endo III, Endo VIII, and mNth1 were incubated with a duplex substrate 25FP/25COM-C containing a Fapy-C pair. Cytosine was chosen as a paired base since Fapy used in this study was originally derived from guanine and a Fapy-C pair could be a naturally occurring base pair. PAGE analysis of the reaction products revealed that treatments with Endo III (Fig. 1A) and Endo VIII (Fig. 1B) resulted in weak bands corresponding to β- and δ-elimination products, respectively, which migrated somewhat slower (β) and faster (δ) than the size marker (M). Although the amount of incision products increased with that of the enzyme and incubation time) were properly adjusted based on the preliminary experiments. Under these conditions, the formation of the product was essentially within a linear (or not saturating) range, thereby allowing direct comparison of the activities for Fapy and Tg (This was also the case for the data in Fig. 3). Table II summarizes the amount of

| Abbreviation | Sequence | Activity Assays for Substrates Containing Fapy and Tg—Duplex substrates (5 nM), 25FP/25COM-N (N = A, G, C, T) and 19TG/19COM-A, were incubated with Endo III, Endo VIII, or mNth1 in appropriate buffers (10 μl) at 37 °C for 5 min. The composition of the buffer for Endo III and Endo VIII was 10 mM Tris-HCl (pH 7.5), 1 mM EDTA, and 100 mM NaCl (buffer A), and that for mNth1 was 20 mM Hepes-KOH (pH 8.0), 50 mM KCl, 0.25 mM EDTA, and 0.25 mM dithiothreitol (buffer B). The amount of the repair enzymes used in the experiments was indicated in the table or figures. To ensure the linear response of the product formation, appropriate amounts of the enzymes and reaction time for the assay were determined by varying these parameters in preliminary kinetic experiments (data not shown). These reaction conditions were used for the activity assays. After incubation, the sample was mixed with gel loading buffer (0.05% xylene cyanol, 0.05% bromphenol blue, 20 mM EDTA, and 98% formamide), heated at 50 °C for 5 min, and separated by 16% denaturing PAGE. The gel was autoradiographed at –80 °C overnight. Alternatively, the radioactivity of the separated bands was analyzed by Fuji BAS 2000.

**Table I**

| Abbreviation | Sequence |
|--------------|----------|
| 15PRM        | 5′-CATCGATAGCATCT |
| 25COM-A      | 3′-GCGATCTTGATGAG |
| 25COM-G      | 3′-GTCATTAGCTGAG |
| 25COM-C      | 3′-AGTCTAGCTGAG |
| 25COM-T      | 3′-GTCATTAGCTGAG |
| 50COM-C      | 3′-AGTCTAGCTGAG |
| 25FP         | 5′-CATCGATAGCATCT |
| 25OX         | 5′-CATCGATAGCATCT |
| 19TG         | 5′-ACGACGCGCAAYCAACCAG |
| 19COM-A      | 3′-TGTGTCGGGATTGTC |

* F = 2,6-diamino-4-hydroxy-5-N-methylformamidopyrimidine (Fapy), O = 7,8-dihydro-8-oxoguanine (8-o xoG), Y = cis-thymine glycol (Tg).
products (i.e., percentage of nicked substrate) for both substrates. Comparison of the yield of products for Fapy and Tg showed that the activity of Endo III and Endo VIII for the Fapy:C pair was approximately 20-fold lower than that for the Tg:A pair, an intrinsic substrate of these enzymes. However, mNth1 recognized both Fapy and Tg equally well.

**Paired Base Effects on the Recognition of Fapy—** It is known that the activity of certain BER enzymes varies depending on the base opposite a lesion. For example, 8-oxoG paired with C and A is excised by Fpg and hOGG1 with different efficiencies (Ref. 29, and references cited therein). The repair activity of Endo III for 5-hydroxypyrimidines (31) and a ring fragmenta-

**TABLE II**

| Enzyme     | Nicked substrate% (Fapy/Tg) | Relative efficiency (Fapy/Tg) |
|------------|----------------------------|------------------------------|
| Endo III   | 55                         | 2.6                          | 0.05                         |
| Endo VIII  | 61                         | 3.4                          | 0.06                         |
| mNth1      | 25                         | 27                           | 1.1                          |

*19TG/19COM-A and 25FP/25COM-C (both 5 nM) containing Tg:A and Fapy:C pairs, respectively, were incubated with Endo III (1 ng), Endo VIII (10 ng), or mNth1 (0.8 ng) at 37 °C for 5 min. The percent of nicked substrate was determined by PAGE analysis.

**FIG. 1.** Reaction products formed in the treatment of the substrate containing a Fapy:C pair with Endo III, Endo VIII, and mNth1. 25FP/25COM-C containing a Fapy:C pair (5 nM) was incubated with varying amounts of Endo III (A), Endo VIII (B), and mNth1 (C) at 37 °C for 5 min, and products were analyzed by PAGE. The amounts of the enzymes used in lanes 1–3 were 1, 5, and 10 ng for Endo III; 10, 20, and 100 ng for Endo VIII; and 0.8, 1.3, and 5 ng for mNth1, respectively. In panels A–C, lanes 4 and 5 show the untreated substrate and a marker (M) prepared by 5'-labeling of 15PRM, respectively. The bands of β- and δ-elimination products are indicated by arrows.

**FIG. 2.** Reaction products formed in the treatment of the substrates containing Fapy:N (N = A, G, C, T) and Tg:A pairs with Endo III, Endo VIII, and mNth1. 25FP/25COM-N and 19TG/19COM-A containing Fapy:N (N = A, G, C, T) and Tg:A pairs, respectively, were incubated with Endo III (A), Endo VIII (B), and mNth1 (C), and products were analyzed by PAGE. The substrates (5 nM) were treated with the enzymes (Endo III (1 ng), Endo VIII (10 ng), and mNth1 (0.8 ng)) at 37 °C for 5 min. The damage in the oligonucleotide (Fapy and Tg), paired base (A, G, C, T) and treatment with (+) and without (−) enzyme are indicated on the top. In panels A–C, lane 1 shows a marker (M) prepared by 5'-labeling of 15PRM. The bands of β- and δ-elimination products are indicated by arrows.

**FIG. 3.** Effects of the paired base on the repair of Fapy by Endo III, Endo VIII, and mNth1. The substrates containing Fapy:N (N = A, G, C, T) and Tg:A pairs were treated with Endo III (A), Endo VIII (B), and mNth1 (C) as described in Fig. 2. The percentage of the nicked substrate was determined by PAGE analysis and plotted against the base pair. The data were the average of three or four independent experiments. Standard deviations are shown by error bars.

**NaBH₄ Trapping of Reaction Intermediates—** The bifunc-
Recognition of Fapy by Endo III Homologues

**Fig. 4. NaBH$_4$ trapping of the Schiff base intermediates.** 25FP/25COM-N and 19TG/19COM-A (both 5 nM) containing Fapy:N (N = A, G, C, T) and Tg:A pairs, respectively, were incubated with Endo III (A), Endo VIII (B), and mNth1 (C) in the presence of 50 mM NaBH$_4$ at 37 °C for 5 min. The amounts of Endo III, Endo VIII, and mNth1 used in the reactions were 5, 20, and 5 ng, respectively. Products were analyzed by 10% SDS-PAGE. The damage in the oligonucleotide (Fapy and Tg), paired base (A, G, C, T) and incubation with (+) or without (−) enzyme are indicated on the top. Free substrates and trapped Schiff base intermediates are indicated in the figure.

**Fig. 5. Effects of the base opposite Fapy on the formation of trapped Schiff base intermediates.** The substrates containing Fapy:N (N = A, G, C, T) and Tg:A pairs were incubated with Endo III (A), Endo VIII (B), and mNth1 (C) in the presence of NaBH$_4$, as described in Fig. 4. The fraction of the substrate converted to the cross-linked product was determined by SDS-PAGE analysis. The percentage of the cross-linked substrate was plotted against the base pair. The data were average of three or four independent experiments. Standard deviations are shown by error bars.

**DISCUSSION**

**Biological Implications of the Fapy Repair Activity of Endo III, Endo VIII, and mNth1—** In the present study, it has been shown that thymine glycol glycosylases from *E. coli* (Endo III and Endo VIII) and mouse (mNth1) have a potential activity to remove the Fapy lesion derived from guanine. Combining the present results and those reported for the *S. cerevisiae* (Ntg1 and Ntg2) (18–20, 22), the repair activity of Fapy is potentially conserved among the thymine glycol glycosylases across species. However, the activity of the *E. coli* enzymes, but not the mouse enzyme, was dramatically influenced by the base opposite this lesion. Endo III and Endo VIII efficiently recognized Fapy when it paired with purines (particularly G in the case of Endo VIII) and very poorly when paired with C (Fig. 3). The very weak activity of Endo III for a Fapy:C pair relative to Tg may explain the reason why Endo III released Tg but not G-derived Fapy from γ-irradiated DNA substrates in the previous study (6) (for A-derived Fapy, see the next section). According to the reported data (19, 22), Ntg1 and Ntg2 recognize Fapy:C pairs in γ-irradiated DNA and methylated/alkali-treated poly(dG-dC) as efficiently as Tg. These results suggest that Ntg1 and Ntg2 resemble the mammalian homologue (mNth1) rather than the *E. coli* enzymes (Endo III and Endo VIII) with respect to the activity for Fapy:C pairs. The substrate specificity of Endo III homologues of *Schizosaccharomyces pombe* (Nth-Spo) (37) and human (hNTH1) (24) has been also examined previously using γ-irradiated or H$_2$O$_2$/Fe-treated DNA. Nth-Spo and hNTH1 released several pyrimidine damages, but neither enzyme released Fapy derivatives from the damaged DNA. Therefore, as far as eukaryotic enzymes are concerned, yeast Ntg1 and Ntg2 but not Nth-Spo recognize Fapy:C pairs, and the mouse (mNth1) but not human (hNTH1)
enzyme recognize Fapy:C pairs. The negligible activity of hNTH1 and Nth-Spo toward Fapy:C pairs was rather surprising since the amino acid sequence of mNth1 shows 81% identity to hNTH1 in 300 overlapping residues and 58.2% identity to Nth-Spo in 226 residues (27). Additionally, all activity assays of mNth1 (this study), hNTH1 (24), and Nth-Spo (37) were performed with recombinant histidine-tagged proteins. An apparent difference in the assay conditions was the enzyme substrate, which contained a single Fapy lesion and multiple types of lesions in the present (mNth1) and previous (hNTH1 and Nth-Spo) studies, respectively. Thus, the influences of co-existing damage in the substrate together with other possible factors need to be assessed to solve the apparent activity difference toward Fapy lesions.

It has been shown previously by transfection studies that Fapy derived from G is lethal but not mutagenic (38, 39), suggesting that G-derived Fapy does not form mispairs with A, G, and T. Thus, as far as G damage is concerned, a Fapy:C pair is the predominant form that repair enzymes encounter in cells. In view of the very weak activity of Endo III and Endo VIII for a Fapy:C pair (20-fold lower than Tg), the activity of these enzymes for a Fapy:C pair may not be physiologically important in E. coli cells relative to Fpg. In contrast, the situation will be different in eukaryotic cells whose Endo III and Endo VIII studies, respectively. Thus, the influences of co-existing damage in the substrate together with other possible factors need to be assessed to solve the apparent activity difference toward Fapy lesions.

The present study has shown that Endo III and Endo VIII, but not mNth1, recognize Fapy in a paired base-dependent manner (Fig. 3). Endo III recognized Fapy:A and Fapy:G pairs most efficiently and a Fapy:C pair least efficiently (Fig. 3A). These paired base effects are quite different from those observed for Fpg and hOGG1, which recognize all Fapy base pairs with comparable efficiencies (29). Endo III excises a variety of pyrimidine lesions, and a common feature of these substrates is the loss of aromatic character due to saturation of the C5-C6 double bond (e.g. pyrimidine glycols and photohydrates), ring fragmentation (e.g. uracil and β-ureidopyrimidinuric acid residues), and ring contraction (e.g. hydantoin derivatives). The structural alterations of these substrates occur along the C4-C5-C6-N1 bonds of the pyrimidine ring. When the structure of Fapy is superimposed on the pyrimidine lesions recognized by Endo III, the ruptured imidazole ring of Fapy overlaps the C4-C5-C6-N1 bonds of the pyrimidine ring. Where the structure of Fapy is superimposed on the pyrimidine lesions recognized by Endo III, the ruptured imidazole ring of Fapy overlaps the C4-C5-C6-N1 bonds of the pyrimidine ring. An example for Tg is shown in Fig. 7A, where the deoxyribose moieties of Fapy and Tg were primarily superimposed to reflect the DNA structure. Thus, the ruptured imidazole ring mimics a defective pyrimidine. It is possible that Endo III potentially senses this feature of Fapy for the initial stage of damage recognition. Concerning the paired base effects, a Fapy (derived from G):C pair is likely to form hydrogen bonds similar to a G:C pair, albeit weaker, since the functional groups involved in hydrogen bonding remain intact in Fapy (Fig. 7, B and C). This notion is also supported by the theoretical calculation of the stabilization energy of the Fapy:C pair (41). Since Endo III uses a flip-out mechanism (42), the stabilization of the Fapy:C pair by hydrogen bonds may retard the extrusion of the Fapy residue into the active site pocket that is suggested to accommodate a flipped out base. Considering that A-derived Fapy was not excised by Endo III from γ-irradiated DNA (6), similar stabilization may occur for a base pair between A-derived Fapy and thymine. Conversely, if a bulky
purine is placed opposite Fapy, the steric clash between Fapy and the purine in a helix extrudes the Fapy residue into a partially extrahelical position, a geometry like in a pretransition state of base flipping. A presumable disposition of a Fapy-G pair is shown in Fig. 7 (D and E). Accordingly, the lack of stabilizing hydrogen bonds and partial extrusion of the Fapy residue facilitate excision of Fapy paired with purines.

Endo VIII showed a paired base specificity similar to Endo III though activity to a Fapy-A pair was lower than a Fapy-G pair (Fig. 3B). Endo VIII is a functional homologue of Endo III, but its amino acid sequence shows no homology to Endo III (8, 9). The overlapping substrate specificity including Fapy pairs between Endo III and Endo VIII implies that Endo VIII employs a damage sensing mechanism similar to Endo III, though the final products formed by the AP lyase activity of Endo III and Endo VIII are different (β- and δ-elimination products, respectively). In contrast to Endo III and Endo VIII, mNth1 exhibited a consistently high activity for all Fapy base pairs (Fig. 3C). The distinctive activities of Endo III and mNth1 for Fapy pairs are rather surprising since the fundamental architecture and catalytic mechanism are predicted to be conserved between Endo III and mNth1 based on the amino acid sequence homology and the characteristic HhH and 4Fe-4S motifs (27), as well as the formation of common Schiff base intermediates (Fig. 4C). The present results suggest that, upon binding to DNA, mNth1 may induce extra structural perturbations in DNA such as kinks or bends over Endo III to extrude the Fapy residue from a stable Fapy:C pair. Currently we do not know the exact origin of such extra perturbations conferred by mNth1. The answer to this question must await for determination of three-dimensional structures of DNA-protein binary complexes of mNth1 and Endo III.

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