A New Class of DNA Glycosylase/Apurinic/Apyrimidinic Lyases That Act on Specific Adenines in Single-stranded DNA*

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Although the biological function of DNA glycosylases is to protect the genome by removal of potentially cytotoxic or mutagenic bases, this investigation describes the existence of natural DNA glycosylases with activity on undamaged, nonmispaired bases. Gelonin, pokeweed antiviral protein, and ricin, previously described as ribosome-inactivating proteins, are shown to damage single-stranded DNA by removal of a protein-specific set of adenines and cleavage at the resulting abasic sites. Using an oligonucleotide as the substrate reveals that the reaction proceeds via the enzyme-DNA imino intermediate characteristic of DNA glycosylase/AP lyases. The adenine glycosylase activity on single-stranded DNA reported here challenges the concept that a normal base has to be in a mismatch to be specifically removed. By contrast to other glycosylases, these enzymes are expected to damage DNA rather than participate in repair processes. The significance of this DNase activity to the biological function of these plant proteins and to their toxicity to animal cells remains to be determined.

Ricin and other related plant proteins such as abrin, gelonin, pokeweed antiviral protein (PAP),¹ and trichosanthin have been classified as ribosome-inactivating proteins (RIPs) in reference to the fact that they inhibit protein synthesis by inactivation of the ribosomes (1). The molecular mechanism of inactivation, elucidated in a cell-free system by Endo and colleagues (2), is the removal of a specific adenine of the 28 S rRNA. This damage, which has been shown to occur in RIP-treated cells, has been generally accepted as responsible for cytotoxicity (1). However, in Plasmodium falciparum-infected erythrocytes, intoxication by gelonin was reported to be associated with the elimination of the parasite 6-kb extrachromosomal (mitochondrial) DNA (3). Moreover, some reports of anti-viral or anti-tumor activities of RIPs also suggest the possibility of additional cytotoxic pathways (4–6).

The weak activity of RIPs in cleaving and linearizing supercoiled, double-stranded DNA in vitro (7–10) has not been given serious consideration because of concerns about contaminating nuclease in the protein preparations. More recent reports have described a preference for single-stranded (ss) DNA (11, 12). The polypeptide responsible for the (zinc-activated) degradation of linear ssDNA by preparations of gelonin, from both native and recombinant bacterial sources, has been identified as gelonin by zymography (12). Conflicting conclusions have been reached on the possible mechanism of DNA degradation. On the basis of the observation that the nicked and linear forms generated by the action of RIPs on supercoiled DNA were not labeled by 3H-labeled sodium borohydride, unlike the fragment generated by the action on rRNA (10), it was suggested that RIPs do not act by a DNA glycosylase mechanism (13). Because boiling ricin-A totally destroyed the activity on 28 S rRNA but only reduced the ability to cleave DNA, the activities were described to be independent (9). Stirpe and co-workers (14), however, suggested that DNA breakage could spontaneously occur because of the weakening produced by the removal of adenines. In this investigation, our primary aim was to study the mechanism of DNA degradation of dsDNA by different RIPs, to reconcile, if possible, the recent descriptions of RIPs as polynucleotide:adenosine nucleosidases (15), polynucleotide:adenosine glycosidases (16, 17), and endonucleases (7–9, 11, 12). The results reveal a new class of DNA glycosylase/AP lyases that act on specific adenines in ssDNA.

EXPERIMENTAL PROCEDURES

Proteins—Gelonin and ricin were purchased from Sigma. PAP was purchased from Worthington Biochemicals Corporation (Freehold, NJ). The proteins were dialyzed against 10 mM HEPES, pH 7.5, prior to use. Protein concentration was determined by reaction with bicinchoninic acid (Pierce) using albumin as a standard.

DNA and Oligonucleotides—The pUC18 DNA plasmid and the 100-bp ladder were obtained from Life Technologies, Inc. The oligodeoxyribonucleotides 28GR-A25 (5'-GTGGGCTCTGCCTGGGTTTCTTCCGATC-3'), 28P-A14 (5'-TGGCGCTTCGGGGATCTCGCTTCGGCGG3'), 28GR-U25, and 28P-U14 (5'-TGCCGGCTCGGGGATCTCGCTTCGGCGG3') were purchased from Biosource International (Camarillo, CA). [α-32P]dATP, [γ-32P]dATP, and Sequenase™ T7 polymerase were purchased from Amersham Pharmacia Biotech; T4 polynucleotide kinase was from Promega (Madison, WI); HindIII, Asp700, and G-25 Quickspin columns were from Boehringer Mannheim; uracil-DNA glycosylase (UDG) was from New England Biolabs, Inc. (Beverly, MA); Trevigen™ 500 was from Trevigen (Gaithersburg, MD); and SDS-PAGE precast gradients gels (4–20%) were from Bio-Rad.

Preparation of Substrates and Standards—Linear pUC18 DNA was prepared by incubation with HindIII, phenol/chloroform extraction, and ethanol precipitation. The concentration was determined by absorption spectroscopy. The HindIII-Asp700 restriction fragments generated from pUC18 were labeled with [α-32P]dATP and Sequenase™ T7 polymerase. The 791-bp fragment labeled at the 3' end of the HindIII site served as a positive control. 4% polyacrylamide gel. In some instances, 7 mol % of the radioactive fragment was added to unlabeled, linear pUC18 DNA. ssDNA was prepared by heat denaturation as described in Ref. 12. The ODNs were 5' end-labeled with T4 polynucleotide kinase and [γ-32P]dATP. The mixture reaction was loaded onto a G-25 Quickspin column equilibrated in 10 mM HEPES, pH 7.0, to remove the unincorporated label. In the assays with ODNs, activity was assayed by the inclusion of 1 mol % 32P-ODN with the unlabeled ODN.

RIP Activity on pUC18 DNA—The amounts of protein and DNA are
indicated in the figure legends. Reactions were carried out in 10 mM HEPES, pH 7.5, 0.1 mM ZnSO₄, and the products were resolved by gel electrophoresis in 16 mM HEPES-KOH, 16 mM sodium acetate, 0.8 mM EDTA (18). For the inhibition study with NaBH₄, a stock solution (1 mM) was freshly prepared immediately prior to use. Assays were performed in the presence of 10 mM NaBH₄ or 10 mM NaCl. To assay for DNA glycosylase activity in the absence of detectable cleavage, a post-treatment with alkali (0.2 M NaOH, 50 mM EDTA, 30 min, 4 °C) was performed before electrophoresis. When the radioactive fragment was included in the reaction mixture, assays were terminated by addition of formamide loading dye for direct loading onto a 15% acrylamide-urea gel for electrophoresis in TBE buffer (89 mM Tris-base, 89 mM boric acid, 2 mM EDTA) and autoradiography. To determine the location of the DNA cleavage sites, the products of the Maxam-Gilbert sequencing reactions (19) on the radioactive fragment were run as markers.

**RIP Activity on ODNs**—1 µg of gelonin or PAP or 2 µg of ricin, in 10 mM HEPES, pH 7, 0.1 mM ZnSO₄, was incubated at 37 °C for 1 h with the appropriate oligonucleotide in a reaction volume of 10 µl at protein/DNA molar ratios of 2:1. To assay for DNA glycosylase activity in the absence of spontaneous cleavage, a post-treatment with 10 mM spermidine for 30 min at 37 °C was performed. Assays were terminated by addition of formamide loading dye for direct loading onto a 15% polyacrylamide-urea gel for electrophoresis in TBE buffer and autoradiography.

The trapping assay was adapted from Ref. 20. The oligonucleotides were added after a preincubation for 5 min at 37 °C of the proteins in the reaction buffer used above but supplemented with 10 mM NaCl or NaBH₄. After 5 min at 37 °C, the samples were post-treated with spermidine as above and subjected to SDS-PAGE on a polyacrylamide 4–20% gradient gel after addition of loading buffer (0.1M sodium phosphate, pH 6.0, 4% SDS, 10% glycerol, 2% β-mercaptoethanol, 0.01% bromphenol blue) and boiling. The gel was fixed, Coomassie-stained, photographed, and analyzed by autoradiography.

**Illustrations**—Photographs and autoradiograms were scanned using a Hewlett Packard Scanjet 4C and processed with Adobe Photoshop 3.0.

### RESULTS

**Degradation of Single-stranded DNA by RIPs**—RIPs have been divided into two classes according to their structure. Class I-RIPs are single-chain, basic proteins with a molecular mass of about 30,000 daltons. Class II-RIPs are neutral proteins composed of two dissimilar chains, of approximately 30,000 Da each, connected by a disulfide bridge. Their active chain is homologous to the class I-RIPs (1). In this study, three RIPs were used. Gelonin and PAP belong to class I, whereas ricin belongs to class II. We have previously reported that ssDNA was the preferred substrate for the nuclease activity of gelonin and that this activity was modulated by zinc (12). Fig. 1A shows that PAP (lane 3) and ricin (lane 4), like gelonin (lane 2), degraded ssDNA in the presence of zinc. On a molar basis, the activity was gelonin > PAP > ricin.

**Formation of Abasic Sites Is the First Step in the Degradation of ssDNA by RIPs**—Electrophoresis on agarose gels under non-denaturing conditions has been widely used to demonstrate the activity of various RIPs in supercoiled (7–9, 13) or linear (12) ssDNA. The appearance of nicked and linear forms or smears was indicative of backbone cleavage. Our first aim was to determine whether the removal of adenosines by RIPs described by Barbieri et al. (14) is the first event in the degradation of ssDNA. The presence of abasic sites is commonly demonstrated by their conversion to nicks upon treatment with alkali (21). Fig. 1B shows the effect of RIPs on ssDNA under conditions of limited reaction when compared with Fig. 1A. The appearance of a smear only after post-treatment with alkali, was indicative of the existence of intermediates. Assays, unlike those in Fig. 1B, were as in A except that the reaction time was limited to 3 min, and the protein concentrations were reduced 2-fold. The products were analyzed without (lanes 1–4) or with (lanes 6–9) a post-treatment (PT) with alkali. C, conditions were as in A except that 10 mM NaBH₄ was present during the reaction. Lanes M contained a 100-bp ladder. The arrow indicates the position of the 600-bp fragment.

**Excision of a Protein-specific Set of Adenines and Strand Scissions at the Resulting Abasic Sites**—To identify the bases removed by the DNA glycosylase activity of the RIPs, the electrophoretic mobilities of the alkali-catalyzed, β-elimination products can be compared with those of the products obtained by the Maxam-Gilbert sequencing procedure (19). To apply this strategy, a 32P end-labeled radioactive fragment of pUC18 DNA was included in the reaction mixture. The reaction conditions were chosen so that the alkali post-treatment was performed on intermediates containing abasic sites but no nicks (data not shown). Electrophoresis in Tris/borate/EDTA did not cleave these intermediates (data not shown). In Fig. 2A, which shows a portion (C90-T105) of the autoradiogram of the sequencing gel, it was seen that the bands revealed by alkali treatment containing primed breaks at sugars without adenosine. Each protein had a specific set of targets. Gelonin and ricin had similar cleavage patterns, removing adenosines 54, 38, 49, 64, and 73. PAP, in addition to adenosines 64 and 73, also excised adenosines 55, 67, and 82. The excision of 5 adenosines of the 17 available between C30 and T105 may explain the appearance of smears in Fig. 1A, which were suggestive of a sequence-
markers. Only a portion of the autoradiogram is shown. 28GR and 28P DNA fragments from Maxam-Gilbert sequencing reactions were run as lanes 2 (and PT) or with 8 pmol of gelonin (lane 2), or with 0.3 pmol of linear pUC18 and 0.02 pmol of a intermediate with NaBH4 (22) and visualized by autoradiography (Fig. 2). The products were analyzed by electrophoresis on a sequencing gel directly (A) or after post-treatment with spermidine (B). The signals were compared with the signals obtained by treatment of 28GR-U25 or 28P-U14 with UDG (lanes 1, 2, 7, and 8). Aliquots containing 6,000 cpm were loaded except in B, lanes 1, 2, 4, 7, 8, and 11, which contained only 2,000 cpm.

Activity on ODNs and Evidence for an Imino Intermediate—A major distinction between simple DNA glycosylases and DNA glycosylase/AP lyases is that the latter group uses an amino group as the nucleophile to attack the sugar of the damaged base nucleotide (22, 24), whereas the former use a hydroxide ion or an associated water molecule. The glycosylase/AP lyase pathway (22) that the imino intermediate could be reversed after base removal so that no strand break would occur, the possibility of its formation was investigated using a

FIG. 2. Evidence of sequence-specific removal of adenines and scission at the abasic sites. Incubations were performed as in Fig. 1A with 0.3 pmol of linear pUC18 and 0.02 pmol of a -800-bp 3' end-labeled fragment of pUC18 as substrates in the absence of protein (lane 1) or with 8 pmol of gelonin (lane 2) or PAP (lane 3) or 32 pmol of ricin (lane 4). The products were analyzed by electrophoresis on a 6% sequencing gel after a short incubation (15, 2, 5, or 15 min for lanes 1-4, respectively) and post-treatment (PT) with alkali (A) or after 60 min (lanes 2 and 3) or 90 min (lanes 1 and 4) without post-treatment (B). The DNA fragments from Maxam-Gilbert sequencing reactions were run as markers. Only a portion of the autoradiogram is shown. 28GR and 28P indicate the fragments used to design 28GR-A25 and 28P-A14.

unspecific mode of degradation. An extended incubation of DNA with RIPs, without chemical post-treatment, also fragmented the substrate (Fig. 1A; Refs. 7-9, 11-13). The products generated under these conditions had the same electrophoretic mobilities as the products generated by alkali-catalyzed β-elimination (Fig. 2B). This indicated that the cleavage occurred at the 3' side of the abasic sites. Glycosylase/AP lyases cleave the phosphodiester bond 3' of the abasic site via a β-elimination reaction (22). The results in Figs. 1 and 2 suggested that the RIPs were DNA glycosylases that had an associated weak AP lyase activity.

Activity on ODNs and Evidence for an Imino Intermediate—A major distinction between simple DNA glycosylases and DNA glycosylase/AP lyases is that the latter group uses an amino group as the nucleophile to attack the sugar of the damaged base nucleotide (22, 24), whereas the former use a nucleophile from the medium, most likely a hydroxide ion or an associated water molecule. The glycosylase/AP lyase activity of the RIPs on ODNs. The preference of gelonin for A25 of 28GR over A14 of 28P and of PAP for A14 of 28P over A25 of 28GR was as predicted from the analysis of Fig. 2. To confirm the hypothesis of adenine removal, the products were analyzed after post-treatment with the β-elimination catalyst spermidine (Fig. 3B). As expected, incubation of gelonin with 28GR-A25 (2:1 molar ratio) and post-treatment with spermidine (lane 4) totally converted the 28-mer into a labeled product that co-migrated with the product of the incubation of UD G with 28GR-U25 (lane 2). Incubation of PAP with 28P-A14 produced a smear similar to the one produced by incubation of the simple glycosylase UDG with 28GR-U25 (lane 2). Incubation of PAP with 28P-A14 produced a smear similar to the one produced by incubation of UD G with 28P-U14 (data not shown). These smears, ascribed to the instability of electrophoresis of abasic site containing oligonucleotides (29), were suggestive of adenine-DNA glycosylase activity on the ODNs. The preference of gelonin for A25 of 28GR over A14 of 28P and of PAP for A14 of 28P over A25 of 28GR was as predicted from the analysis of Fig. 2. To confirm the hypothesis of adenine removal, the products were analyzed after post-treatment with the β-elimination catalyst spermidine (Fig. 3B). As expected, incubation of gelonin with 28GR-A25 (2:1 molar ratio) and post-treatment with spermidine (lane 4) totally converted the 28-mer into a labeled product that co-migrated with the product of the incubation of UD G with 28GR-U25 and post-treatment with spermidine (lane 2), whereas incubation of PAP with 28P-A14 and post-treatment with spermidine (lane 11) produced a band that co-migrated with the product of the incubation of UD G with 28P-U14 (lane 8). The activity of gelonin on 28P-A14 (lane 10) was low, as was the activity of PAP on 28GR-A25 (lane 5). Ricin had a detectable glycosylase activity on A25 of 28GR (lane 6). It was concluded from Fig. 3 that RIPs remove adenine from single-stranded 28-mers with preferences similar to that observed with an 800-base substrate. There was no evidence of AP lyase activity on the ODNs.

Because it has been proposed in the model for the glycosylase/AP lyase pathway (22) that the imino intermediate could be reversed after base removal so that no strand break would occur, the possibility of its formation was investigated using a
NaBH₄ trapping assay (Fig. 4). 28GR-A25, shown to be a substrate for all three RIPs in Fig. 3, was used as the substrate. The RIP/ODN molar ratio of 2:1, similar to the one used in Fig. 3, was in the range of the ratios used in Ref. 22 to demonstrate the validity of the borohydride trapping assay for distinguishing between the simple glycosylases and the glycosylase/AP lyases. The 2:1 ratio was 50 times lower than was used to demonstrate the formation of the MutY-DNA intermediate (25). Experiments aimed at defining the trapping assay conditions indicated that 10 mM was a suitable concentration of NaBH₄ or NaCl to be used with gelonin and PAP because the presence of 10 mM NaBH₄ during the incubation totally inhibited the alkali sensitivity, whereas cleavage was obtained with 10 mM NaCl (data not shown). This concentration was also used with ricin, despite the observation that 10 mM NaCl greatly reduced the glycosylase activity, since 10 mM NaBH₄ was determined to be the minimal concentration required to inhibit the alkali sensitivity (data not shown). The electrophoretic mobility of the proteins is shown in Fig. 4A. The bands of reduced mobility detected by autoradiography (Fig. 4B) were consistent with the NaBH₄ trapping of covalent gelonin-ODN (lane 2) and PAP-ODN (lane 4) complexes. The absence of signal in lane 6 was not unexpected, given the weak glycosylase activity of ricin. Surprisingly, the presence of NaBH₄ did not appear to be an absolute requirement for complex detection, especially in the case of gelonin (lane 1). Complexes of similar molecular mass were also detected as minor reaction products, with all three RIPs, when aliquots of the samples previously analyzed by sequencing gel (Fig. 3) were analyzed by SDS-PAGE (data not shown). Formation of complexes via a Schiff base between depurinated DNA and proteins (e.g. histones) that were stable at neutral pH have been observed previously (30). However, the detection of RIP-ODN complexes was unexpected, given that stabilization of the transition states by modification of the substrate or the enzyme is usually required to observe complexes between DNA and catalytic DNA binding proteins (31, 32).

**DISCUSSION**

**A New Class of DNA Glycosylase/AP Lyases**—On the basis of the results of our investigation, the RIPs meet the established criteria (22, 24) to be classified as DNA glycosylase/AP lyases. The description of a DNA glycosylase/AP lyase activity on ssDNA is unique, because UDGs, which are the only described DNA glycosylases with in vitro activity on ssDNA, do not have an associated lyase activity (21). As was the case for several other DNA glycosylases (33), the associated AP lyase activity that nicks DNA at the site of base removal led to the description of RIPs as “endonucleases.” In our investigation, the lyase activity was evident when full-length, single-stranded pUC18 (Fig. 1) or an 800-base fragment (Fig. 2) were used as substrates. The ability to detect intermediates containing abasic sites but no nicks (Figs. 1 and 2) suggested that, similar to the pyrimidine dimer-glycosylase/AP lyase T4 endonuclease V (34), the AP lyase activity was weak. ODNs were substrates for adenine-DNA glycosylase activity but were not cleaved (Fig. 3). To our knowledge, this is the first report of the absence of AP lyase activity of a native DNA glycosylase/AP lyase on an unmodified ODN. Chemical attachment of a fluorine atom at the 2΄ position of the 5΄ component of a thymine dimer site has been shown to inhibit the strand cleavage, but not the glycosylase activity, by T4 endonuclease V (31). Our results suggest that the classification of enzymes as simple DNA glycosylases or DNA glycosylase/AP lyases should not rely solely on assays using oligonucleotides as substrates nor the NaBH₄ trapping procedure.

The proposed mechanism for the DNA glycosylase/AP lyase pathway (24) predicts that the fate of the covalent imino intermediate is to be hydrolyzed, either before or after the DNA undergoes a β-elimination reaction, resulting in scission of the phosphodiester backbone. Dissociation of the intermediate before the β-elimination reaction could explain the absence of detectable levels of scission products in Fig. 3A. The cleavage of the 3΄-C-O bond occurs after enzyme-assisted abstraction of the 2΄-H (31, 35, 36). An alternative explanation for the absence of cleavage of ODNs by RIPs despite base removal, which takes into account the observation of formation of stable complexes in the absence of NaBH₄, could be that an essential residue, such as Glu239 of T4 endonuclease V (35, 37) cannot play its role in β-elimination but instead stabilizes the intermediate. The removal of a RIP-specific set of adenesines has been established in Figs. 2 and 3. Whereas certain engineered mutations in the active site of human UDG resulted in novel enzymatic activities that released normal pyrimidines from DNA (38), RIPs are the first natural glycosylases able to remove normal bases from DNA. With their unique ability to excise a specific set of undamaged bases from single-stranded DNA, RIPs should be of interest for structural biologists investigating the basis of base recognition by DNA glycosylases, because their activity challenges the concept that a normal base has to be in a mismatch to be specifically removed. Moreover, RIPs could, similarly to UDG, have practical applications in molecular biology.

**The Physiological Function of RIPs and the Consequences of DNA Glycosylase Activity on Normal Bases in Mammalian Cells**—The proteins used in this study are from plants. They are known as ribosome-inactivating proteins, but their physiological function is not clear (1). A possible role of RIPs could be in adenine metabolism, because enzymes that catalyze cleavage of the N-glycosidic bond in nucleotides, nucleosides, or related compounds are central to salvage pathways. The observation of their induction upon stress or senescence (39) suggests that they could be involved in macromolecular turnover. Viral infection of sugar beets has been shown to induce the expression of RIPs (40). Although DNA glycosylases can be seen as defenses against potentially injurious modifications of DNA, RIPs now described as adenine-ssDNA glycosylase/AP lyases could have a protective function by damaging the genetic material of invading pathogens.

In addition to uses in agricology (41), RIPs are being evaluated for their anti-cancer (42) or anti-viral efficacy in humans (43). Some reports have suggested that their effects may not be (only) because of inhibition of protein synthesis (3–6). The observations of selective inhibition of viral DNA synthesis by PAP (4) or elimination of the parasite 6-kb extrachromosomal (mitochondrial) DNA of *P. falciparum* infected erythrocytes by gelonin (3) are consistent with a DNA damaging activity of RIPs. The characterization of the activities on DNA of proteins such as the C-terminal deletion mutant of PAP that inhibits
viral infection but does not depurinate host ribosomes (6) might give a better insight into the origin of their anti-viral effect.

DNA glycosylases are classically described as enzymes of the DNA repair pathway (44). In the last few years, it has become clear that defects in genes that maintain the integrity of the genome may be causes of inherited predispositions to cancer (45). The expression of these proteins until their physiological role and cytotoxic pathways are better characterized.

A New Name for RIPs?—Plant RIPs are a family of enzymes whose physiological function is unknown and whose pharmacological activities do not appear to be solely because of the “classical” property of inhibitors of protein synthesis after which they were named. On the basis of activities observed on various substrates in vitro, it had been proposed to reclassify them as polynucleotide-adenosine deaminases (15) or polynucleotide:adenosine glycosidases (14, 16). These terminologies appear to be inappropriate. We propose to postpone the renaming of these proteins until their physiological role and cytotoxic pathways are better characterized.

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