In Vitro Bypass Replication of the Cisplatin-d(GpG) Lesion by Calf Thymus DNA Polymerase β and Human Immunodeficiency Virus Type I Reverse Transcriptase Is Highly Mutagenic*

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Eukaryotic DNA polymerase β and the reverse transscriptases are the most inaccurate of the known DNA polymerases. We report here mutagenic replication in vitro past intrastrand N(7)G-N(7)G chelates of the cis-diamininedichloroplatinum(II), the major DNA adduct of the antitumor agent cisplatin by calf thymus DNA polymerase β and human immunodeficiency virus type I reverse transcriptase (42% and 26% mutations, respectively). The most frequent modifications generated by both enzymes were one-base frameshift deletions. Only one mutational hot spot opposite the platinated guanines was observed with human immunodeficiency virus type I reverse transcriptase, while two hot spots were generated by DNA polymerase β, one at the base situated 5’ to the lesion and the other situated 4–6 nucleotides 5’ to the adduct. An unusual mutagenic event, tandem replication of a 12-base pair sequence, was observed with DNA polymerase β. The mutational spectra of the two DNA polymerases suggest that template slippage occurred with higher frequency in the presence of the more distributive DNA polymerase β.

The molecular mechanisms of mutagenesis are not well understood. One general pathway is thought to involve error-prone replication past unrepaired DNA damage. Bulky DNA lesions can result from cellular exposure to agents such as UV light or a variety of chemical carcinogens. Studies performed in vivo indicate that mammalian cells possess the ability to circumvent blocks to DNA synthesis and are able to replicate in vivo the presence of these lesions (1–4).

Enzymes and Chemicals—Calf thymus DNA polymerase β was purified as described previously (16) and was a generous gift of Drs. Vladimir Podust and Ulrich Hübscher (Zurich, Switzerland); 1 unit of DNA polymerase β corresponds to 1 nmol of dNTP incorporated into acid-insoluble materials at 37°C in 60 min. HIV-1 RT was purified according to Preston et al. (17) and was generously provided to us by Dr. Lawrence Loeb (Seattle, WA).

PMaterials and Methods

Bacteria—Escherichia coli MC1061 (hsdR, mcrB, araD, 139Δ (araABC-leu), 7679ΔlacX74, galU, galK, rpsL, thi, lacX74, galU, galK, rpsL, thi), used as an indicator for the transfected E. coli MC1061, were provided by Dr. Lawrence Loeb (Seattle, WA).

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1The abbreviations used are: Pt-d(GpG), intrastrand N(7)G-N(7)G chelates of the cis-diamininedichloroplatinum(II); HIV-1, human immunodeficiency virus; RT, reverse transcriptase; pol b, DNA polymerase β; adjacent guanine bases of codon 13 of the human HRAS gene.

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5'-dTCAACCAAGAGCATAC-3' was labeled at its 5' terminus using (\gamma^{32}P)ATP and annealed to the 60-mer and the 60-mer platinum-containing templates. Labeled primed-templates (100 ng) were extended in vitro by 50 units of calf thymus DNA polymerase \( \beta \) or 40 units of HIV-1 RT at 37 °C for 120 min in 10 independent samples of 15 μl for each enzyme. DNA synthesis was terminated by the addition of stopping buffer, and the replicated DNA was heat-denatured and resolved by electrophoresis through a 15% polyacrylamide, 7 M urea, 30% formamide gel. The bypass products were then excised from the gel, and the DNA extracted overnight at room temperature in presence of 300 μl NaCl and centrifuged through a Sephadex G-50 minicolumn to remove salts and unincorporated (\gamma^{32}P)ATP.

Analysis of Reaction Products by Polymerase Chain Reaction (PCR) and DNA Sequencing—Approximately 0.1 ng of the purified bypass product (bypass 1 and 2, Fig. 4A; and bypass product, Fig. 4B) were mixed with 30 pmol each of PCR primers; a 27-mer primer (5'-GAATTCACAACCAAGAGCATACGACGGG-3'), which complemented positions 39–59 of the 60-mer and bore an EcoRI restriction site, and a 22-mer primer (5'-GGGGTACCGTGCGGACCCG-3'), which corresponded to nucleotides 1–13 of the 60-mer and bore a BamHI restriction site. Amplification was obtained in a final volume of 50 μl containing 10 mM Tris-HCl (pH 8.3), 50 mM KCl, 1.5 mM MgCl₂, 1 μM each of dATP, dCTP, dGTP, and dTTP, and 1 unit of AmpliTaq DNA polymerase. The reaction mixtures were heated to 95 °C for 1.5 min, followed by 30 cycles of 94 °C (1 min), elongation (72 °C, 1.5 min), and denaturation (95 °C, 30 s). The PCR products were visualized on a 2% agarose gel containing ethidium bromide and resolved by extraction with phenol/chloroform/isoamyl alcohol, followed by precipitation with ethanol. The PCR products were then digested with EcoRI and BamHI, ligated into the polylinker region of M13mp10 using 1 unit of DNA ligase, and incubated overnight at 16 °C. E. coli MC1061 were electrotransformed in the presence of 4 μl of ligation reaction at 2 kV, 25 microfarads, and 200 ohms using a GenePulser electroporator (Bio-Rad). The transformed cells were plated with E. coli CSH50 cells. Colorless plaques were picked, single-stranded DNA was prepared, and the inserted DNA segments were sequenced (18).

Quantitative Determination of the Replication Products Generated by HIV-1 RT and DNA Polymerase \( \beta \) on Intact or Platinated Templates—After replication, the products were resolved by electrophoresis through a 15% polyacrylamide, 7 M urea, 30% formamide gel. The autoradiograms were then scanned using a Whole Band Analyzer version 3.2.2, and the bands were quantified with the Bioimage \( \beta \) application (Rassy-France).

RESULTS

HIV-1 Reverse Transcriptase Can Replicate Efficiently Past the Pt-d(GpG) Lesion—We annealed the 60-mer and the 60-mer platinum-containing templates with a 5'-phosphorylated 17-mer oligonucleotide primer (Fig. 1A) and investigated primer extension by different amounts of enzyme and at different incubation times. The newly synthesized DNA products were resolved by polyacrylamide gel electrophoresis and visualized by autoradiography. Fig. 1B shows the replication of 10 ng of intact and treated oligonucleotides by increasing amounts of enzyme. Full-size (60-mer) products were observed after replication of unplatinated template by all HIV-1 RT concentrations tested, although about half of the available primers were not processed by the enzyme at the highest enzyme concentration. An intermediate product, located at a GGG run (nucleotides 10–12 of the template sequence; indicated by an asterisk in Fig. 1B, left lanes) was also observed, indicating the presence of a replicative pause during polymerization. Two classes of reaction products were observed after replication of the cisplatin-damaged template (Fig. 1B, right lanes). The products migrating as 39-, 40-, and 41-mers correspond to arrest of replication either at the base preceding the lesion or at the bases opposite the platinumated guanines. The other products are roughly located at the position of the full-size template. The amount of bypass products increased with the concentration of HIV-1 RT, reaching 53% of the elongated products in presence of 1 unit of enzyme (Fig. 1C). A kinetic study, performed with 1 unit of HIV-1 RT for incubation times ranging from 5 to 60 min gave comparable results (data not shown). The pause site observed following synthesis on undamaged template (asterisk in Fig. 1B, left) was less intense when replication occurred on the platinumated 60-mer (see also Fig. 2), suggesting that HIV-1 RT dissociated less frequently at the (GGG) run when the indicated amounts of HIV-1 RT. Arrows indicate the position of the primer (17-mer), reaction products (60-mer), and products terminated at the lesion (39-mer). The bracket shows the position of the two platinumated guanines in the template and the T preceding them. The asterisk indicates the site of replicative pause by HIV-1 RT at the GGG run in the template. C, quantitative analysis of the frequency of bypass replication by HIV-1 RT on the damaged template. The amount of bypass products was determined for the three indicated amounts of enzyme as described under "Materials and Methods" and given as percentage of the total elongated products.

Fig. 1. Bypass synthesis by HIV-1 RT during in vitro DNA replication of 60-mer-Pt substrate. A, the 60-mer substrate annealed to a 17 base oligonucleotide primer. P, indicates the intranstrand bifunctional Pt-d(GpG) adduct. B, effect of increasing amounts of enzyme on primer extension; 10 ng of intact and damaged substrates were replicated for 1 h at 37 °C by the indicated amounts of HIV-1 RT. Arrows indicate the position of the primer (17-mer), reaction products (60-mer), and products terminated at the lesion (39-mer). The bracket shows the position of the two platinumated guanines in the template and the T preceding them. The asterisk indicates the site of replicative pause by HIV-1 RT at the GGG run in the template. C, quantitative analysis of the frequency of bypass replication by HIV-1 RT on the damaged template. The amount of bypass products was determined for the three indicated amounts of enzyme as described under "Materials and Methods" and given as percentage of the total elongated products.

HIV-1 Reverse Transcriptase Can Initiate Replication Opposite the Pt-d(GpG) Adduct—We have shown previously that replicative bypass of the Pt-d(GpG) lesion by calf thymus DNA polymerase \( \beta \) is correlated with capacity of the enzyme to initiate DNA synthesis from the base preceding the lesion (6). To assess the importance of this mechanism for HIV-1 RT, we analyzed its capacity to extend a 39-mer primer, whose 3' dA...
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Terminus was positioned opposite the dT base prior to the lesion (Fig. 2A). Fig. 2B (left lanes) shows that primer extension on the intact template by HIV-1 RT generated a full-length 60-mer product and the intermediate product previously detected (see Fig. 1). The enzyme efficiently initiated DNA synthesis from the nucleotides opposite the Pt-(dGpG) adduct (Fig. 2B, right lanes). Bypass products represented more than 60% of the extended oligonucleotides after 1 h at 37 °C (Fig. 2C). These results suggest that the mechanism enabling in vitro bypass of the Pt-(dGpG) adduct by HIV-RT is similar to the one proposed for DNA polymerase β.

Primer utilization on both platinated and unplatinated templates was greater then for the 17-mer (Fig. 1), perhaps reflecting greater stability of the initiation complex with the annealed 39-mer. As was observed for the 17-mer primed 60-mer platinated template, the intensity of the pause site located at the GGG run was greatly reduced upon replication of the 39-mer primed 60-mer platinated template compared to the intact template (Fig. 3). Hence, the presence of the adduct diminished the pausing of HIV-1 RT, which might suggest a more processive mode of DNA synthesis when replicating the damaged substrate.

PCR Amplification of the Bypass Products Generated by DNA Polymerase β and HIV-1 RT—In order to investigate the fidelity of DNA replication past the Pt-(GpG) adduct catalyzed by DNA polymerase β and HIV-1 RT, we examined the sequences of the high molecular weight bypass products generated by the enzymes. These were resolved by electrophoresis on a polyacrylamide gel, excised, purified, and amplified (see Fig. 4, A and B, and "Materials and Methods" for details). Translesion replication products represented 55% of the extended products with HIV-1 RT, and 72% with DNA polymerase β. As a control, products generated on the undamaged template were also purified in the same way. As can be seen in Fig. 4A, DNA polymerase β generated a second, minor higher molecular weight product after bypassing the cisplatin lesion. This product, designated bypass 2, represented 8% of the elongated products and migrated as a 72-mer according to a M13 sequence reaction products that were loaded on the same gel (not shown). We were able to PCR-amplify the bypass 2 product by using the same PCR primers used to amplify the bypass 1 (see "Materials and Methods").

We found that the single-stranded bypass products migrated at the same position on denaturing gels as the platinated single-stranded templates (data not shown). Consequently, the non-radioactive platinated templates were purified together with the radioactive synthesized bypass products. In order to assure exclusive amplification of the bypass products by PCR, we verified that the Taq DNA polymerase was unable to amplify the damaged templates in the course of the PCR reaction. To do this, the 60-mer undamaged and damaged templates were annealed to 5'-32P-labeled 17-mer primer and replicated by the Taq DNA polymerase at 72 °C for 1.5 min to mimic the first cycle of the amplification reaction. The products of replication by the Taq were then resolved by electrophoresis on a polyacrylamide gel and visualized by autoradiography. The enzyme, which can efficiently elongate the untreated control template, stopped opposite the thymine base immediately preceding the lesion (data not shown). Hence, an abortive product
was obtained, which could not be amplified during the subsequent cycles. This result indicated that the cisplatin-damaged templates present among the population of the bypass products cannot be processed by the Taq DNA polymerase and therefore cannot be PCR-amplified.

Analysis of DNA Sequence in the Bypass Products Generated by Calf Thymus DNA Polymerase b and HIV-1 RT—The PCR-amplified bypass products were cloned into the polylinker region of M13mp10 replicative form DNA so that they created an out-of-frame insert in the lacZ gene. The recombinant DNA was electroporated into MC1061 E. coli cells, and colorless plaques were randomly picked. Single-stranded DNA was prepared, and nucleotide sequences of the bypass products were determined by the dideoxynucleotide chain termination method (18).

No mutations were observed among the 25 clones sequenced from full-size products generated by the DNA polymerase b on the intact template. This demonstrates that the mutations detected on platinated template were caused by DNA polymerase b replication errors during translesion synthesis past the Pt-(GpG) adduct and that no mutagenic events occurred at high frequency during PCR amplification.

Sequencing of 36 recombinant molecules containing bypass 1 products generated in vitro by DNA polymerase b yielded a total mutation frequency of 42%. Table I shows the location, type, number, and relative frequency of mutations obtained. The most frequent modifications were −1 deletions of the cytosine situated immediately in 5' of the two adjacent guanines involved in the cisplatin lesion.

Some of these −1 frameshift modifications were accompanied by one or two additional mutations at the sequence CGCC (template nucleotides 13–16), essentially deletions of cytosines (Table I). The presence of these double and triple mutants suggested that modifications at the first hot spot 5' of the adduct might have promoted mutations at the CGCC sequence. We found three mutants deleted in the cytosine at position 13 of the template, which is the 3'-terminus of the left PCR primer (Table I). These mutations are likely not the result of a PCR artifact, since such mutations were not observed among the clones sequenced as controls. The fact that all these three

![Figure 4](http://www.jbc.org/Downloaded-from)
weaker than that of the intact templates by HIV-1 RT. Sequencing of 42 recombinant molecules containing bypass products generated in vitro by HIV-1 RT yielded a mutation frequency of 26%, less than the frequency observed with DNA polymerase β. In addition, the observed mutation spectrum was different (Table II); most of the modifications were single mutations, and 90% of these (9/10) were at the site of the lesion. Among these modifications, 54% (6/11) were one-base deletions opposite one of the two guanines involved in the adduct, while 27% (3/11) were insertion of T opposite G at position 20. These data demonstrate that the mutagenic consequences of the bypass catalyzed by HIV-1 RT are different from those obtained with calf thymus DNA polymerase β.

FIG. 5. Sequences of the bypass 2 generated by DNA polymerase β. Left, wild type sequence. The two guanines involved in the cisplatin lesion are shown by a bracket. The arrow indicates the position in the wild type sequence where the insertion occurs. Right, sequence of bypass 2 containing the newly inserted sequence (box).

DISCUSSION
cis-Diaminedichloroplatinum(II) (cisplatin) is an anticancer agent that is frequently used in the treatment of testicular and ovarian cancers (19). DNA damage is responsible for the cytotoxic and mutagenic effects of cisplatin, and it has been shown that the Pt-d(GpG) adduct is the most common lesion formed on DNA by this agent (20). This lesion is refractory to repair by crude cell extracts (21, 22), mainly due to protection of the lesion from repair enzymes by high mobility group-domain proteins (23). Cisplatin induces mutations in both prokaryotes and eukaryotes. Thus patients treated with this drug may risk developing secondary tumors (24). A possible mechanism of cisplatin-induced mutagenesis is an error-prone replication past the Pt-d(GpG) adduct. We have recently observed efficient translesion synthesis of this adduct by calf thymus DNA polymerase β (6), the least accurate of the eukaryotic DNA polymerases (9, 25). We show here that, like pol β, HIV-1 RT is able to bypass the same defined Pt-d(GpG) adduct (Fig. 1).

A bulky adduct such as Pt-d(GpG) might be expected to strongly reduce DNA polymerase binding, as suggested by the capacity of Pt-d(GpG) to terminate DNA synthesis by numerous DNA polymerases (6, 26–29). Structural studies of these enzymes suggest that contacts between the protein and template-primers might be severely perturbed by the presence of DNA damage. In contrast, the Pt-d(GpG) adduct did not inhibit replication by HIV-1 RT (Fig. 1) and pol β (6). Both were capable of initiating replication at 3′ terminus across from the lesion, suggesting that the mechanism enabling in vitro bypass may be similar for these enzymes (Fig. 2 and Ref. 6). Furthermore, replication across the Pt-d(GpG) adduct by HIV-1 RT and pol β was highly mutagenic (Tables I and II). To our knowledge, this is the first time that the mutagenic power of the cisplatin has been demonstrated in vitro, and that this property is shown to be the result of translesion synthesis.

We observed that 42% of the replication products of calf thymus DNA polymerase β contained mutations. We found that 26% of these mutations were single-base deletions of the cytosine in 5′ of the lesion and that 60% of the mutagenic events were multiple mutations. Most of these modifications occurred at two hot spots, one situated at the nucleotide dC in 5′ to the cisplatin bifunctional lesion (template nucleotide 19), and the other located at the sequence CGCC (template nucleotides 13–16) (Table I).

It is of interest to compare the mutation spectrum of this adduct in vitro with results in mammalian cells where polymerase β might be expected to be an important element in replicative bypass. A single-stranded DNA vector bearing the same cisplatin-modified HRAS sequence has been replicated in simian COS-7 cells with an observed mutation frequency of 21%. However, in contrast to results with purified DNA polym-
erase β, the most frequent modifications in vivo were base substitutions and 92% of the mutagenic events occurred at one or both of the platinated guanines (3). A direct comparison of these data is difficult, since DNA repair after translesion replication (mismatch repair or loop repair) may substantially alter in vivo results. Furthermore, the discrepancy between the in vivo and the in vitro mutagenesis spectra might be explained by the different stability and topology of the DNA templates used (60-mer oligonucleotide versus single-stranded DNA). Finally, it is entirely possible that bypass replication of the platinated HRAS sequence in vivo requires the action of DNA polymerases other than DNA polymerase β, or the involvement of yet unidentified accessory proteins.

Different frequencies and positions of mutations were obtained with HIV-1 RT (Table II); 26% mutagenesis was observed (compared to 42% with pol β), and mutations were primarily one-base deletions targeted at a hot spot opposite the lesion.

DNA polymerase β, the least processive enzyme, shows a higher propensity for frame shifts in an in vitro M13mp2 mutagenesis assay compared to other DNA polymerases (25). HIV-1 RT also shows a strong tendency to generate frame shifts within runs of three or more of the same nucleotide on M13mp2 DNA (11). Hence, the capacity of both enzymes to produce one-base frame-shift deletions at or near the Pt-d(GpG) adduct was not unexpected. Frame-shift mutations from transient misalignment of the primer-template junction at a DNA lesion have been reported previously (30–33). A similar mechanism of dislocation, induced by the rigid conformational constraint of the Pt-d(GpG) adduct (34), could explain the one-base deletions at the damage after HIV-1 RT replication (Fig. 6A). In the case of DNA polymerase β, however, two correct nucleotides dC were incorporated opposite the platinated guanines (Table I). This result and our previous data (6) suggest that translesion synthesis is more efficient by pol β than by HIV-1 RT. With this enzyme, template slippage appears to occur 5' of the lesion (Fig. 6B).

The unexpected second mutation hot spot observed with calf thymus DNA polymerase β deserves comment (Table I). This site was located at the sequence GGCC, 4–7 nucleotides 5' to the cisplatin adduct. Two types of mutations were detected. First, two-base frameshift deletions appeared at the GGCC hot spot concomitantly with a mutation across from the lesion. Although modification of the replication complex at the lesion may somehow favor a strand slippage at the second hot spot, the reasons for this apparent "two hit" mutagenesis and for the relative positions of the two hot spots are unclear. Second, a 12-nucleotide repeat (nucleotides 3–14 of the template) was observed between dG and dC of the GGCC hot spot with a frequency of 8% of the elongated products (bypass 2, Fig. 4). Further studies with other DNA lesions and template sequences will be necessary to determine whether these unusual mutagenic events represent a general phenomenon. If so, damage-induced tandem replication by DNA polymerase β could be an important mechanism for genetic instability.

DNA polymerase β has a distributive mode of DNA synthesis (35) and likely dissociates and reassociates frequently with the substrate. These dissociation events could increase the opportunities for template flexibility and slippage induced by the presence of a bulky adduct. In contrast, higher processivity could explain why HIV-1 RT produced fewer frameshift mutations compared to DNA polymerase β. A correlation between the probability of dissociation from the template of HIV-1 RT and its capacity to generate frameshift has been proposed (36, 37). In spite of a common polymerase folding motif (15), the co-crystal structure of HIV-1 RT showed that the enzyme can bind to a DNA template-primer in an orientation opposite to that of DNA polymerase β (38, 39). This anti-pol β mode of DNA synthesis has been shown to confer processivity to the enzyme (40, 41). Increased processivity of HIV-1 RT is suggested by the observation that this polymerase paused less at the GGG sequence during replication of cisplatin-damaged DNA than while replicating undamaged template (Figs. 1 and 2). Therefore, distributive mode of DNA synthesis could be an important mechanism for DNA damage-induced instability.

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