Lesion Bypass by Human DNA Polymerase $\mu$ Reveals a Template-dependent, Sequence-independent Nucleotidyl Transferase Activity*

Shay Covo‡, Luis Blanco§, and Zvi Livneh¶¶

From the ¶Department of Biological Chemistry, Weizmann Institute of Science, Rehovot 76100, Israel and the §Centro de Biologia Molecular Severo Ochoa (CSIC-UAM), Universidad Autonoma, 28049 Madrid, Spain

DNA polymerase $\mu$ (pol $\mu$), which is related to terminal deoxynucleotidyl transferase and DNA polymerase $\beta$, is thought to be involved in non-homologous end joining and V(D)J recombination. Pol $\mu$ is induced by ionizing radiation and exhibits low fidelity. Analysis of translesion replication by purified human pol $\mu$ revealed that it bypasses a synthetic abasic site with high efficiency, using primarily a misalignment mechanism. It can also replicate across two tandem abasic sites, using the same mechanism. Pol $\mu$ extends primers whose 3'-terminal nucleotides are located opposite the abasic site. Most remarkably, this extension occurs via a mode of nucleotidyl transferase activity, which does not depend on the sequence of the template. This is not due to simple terminal nucleotidyl transferase activity, because pol $\mu$ is unable to add dNTPs to an oligo(dT)$_{20}$ primer or to a blunt end duplex oligonucleotide under standard conditions. Thus, pol $\mu$ is a dual mode DNA-synthesizing enzyme, which can act as either a classical DNA polymerase or as a non-canonical, template-dependent, but sequence-independent nucleotidyl transferase. To our knowledge, this is the first report on a DNA-synthesizing enzyme with such properties. These activities may be required for its function in non-homologous end joining in the processing of DNA ends prior to ligation.

DNA polymerase $\mu$ (pol $\mu$)$^*$ is a recently identified member of the X family of DNA polymerases. Pol $\mu$ shares 41% amino acid identity with terminal deoxynucleotidyltransferase (TdT), a template-independent DNA polymerase (1, 2). In addition, both pol $\mu$ and terminal deoxynucleotidyltransferase are overexpressed in the immune system. However, unlike terminal deoxynucleotidyltransferase, which is specific to the immune system, pol $\mu$ is expressed in additional tissues (1, 2). In vivo analysis with pol $\mu$-deficient mice revealed depletion of B cells in peripheral lymphoid organs in ~50% of the mice and impairment of the immunoglobulin $\kappa$ light chain rearrangement (3, 4). This suggests that pol $\mu$ is essential in V(D)J recombination, at least in mice. In addition, pol $\mu$ is up-regulated in response to ionizing and UV radiation and forms complexes with DNA ligase IV and the Ku proteins (5). This indicates that pol $\mu$ partakes not only in V(D)J recombination but generally in non-homologous end joining (NHEJ). Pol $\mu$ was shown to be an error-prone DNA polymerase (1, 6), capable of incorporating either dNTPs or uNTPs (7, 8). It has an outstanding tendency to form frameshift mutations, directed by its ability to misalign the primer terminus with short downstream homologies (microhomology search) (6). Based on this property, it was proposed that pol $\mu$ functions in NHEJ by searching homology between two broken ends, followed by filling in small gaps.

When DNA is damaged in the vicinity of a break, its processing by DNA synthesis might require lesion bypass. Here we show that, unlike most other DNA polymerases, purified pol $\mu$ bypasses a synthetic abasic site very efficiently. Surprisingly, when extending a primer terminus located opposite an abasic site, pol $\mu$ adds each of the four dNTPs, regardless of the sequence of the template. To our knowledge, this is the first report on a template-dependent but non-instructed nucleotidyl transferase activity.

MATERIALS AND METHODS

Proteins—Recombinant human pol $\mu$ was expressed in Escherichia coli and purified as described (9). E. coli Pol IV (His-tagged) was a generous gift from H. Ohmori (Kyoto University, Kyoto, Japan), and the E. coli pol I Kleng fragment was purchased from U. S. Biochemical Corp.

DNA Substrates—DNA oligonucleotides without a lesion were supplied by Sigma-Genosys, whereas oligonucleotides containing synthetic abasic sites (dSpacer, Glen Research, Sterling, VA), were synthesized by the Synthesis Unit of the Biological Services Department in our institute or purchased from Metabion ( Martinsried, Germany). The DNA substrates used in this study are shown in Fig. 1. They were prepared by annealing a 5'-S'-end-labeled primer oligonucleotide to the template oligonucleotide, followed by purification on a BioSpin 30 gel-filtration column (Bio-Rad) as described previously (10–12). Analysis by electrophoresis on native gels revealed that >95% of the primers were annealed to the template oligonucleotides.

Primer Extension Reactions—A typical primer extension reaction (20 $\mu$l) contained 200 nM Tris-HCl, pH 7.5, 0.1 mM EDTA, 8 mM $\mu$M bovine serum albumin, 4% glycerol, 5 mM dithiothreitol, 5 mM MgCl$_2$, 100 $\mu$M each of dATP, dCTP, dGTP, and dTTP, and 50 nM primed oligonucleotide substrate. Pol $\mu$ or DNA polymerase I (Klenow fragment) at 20–50 $\mu$M were added to start the reactions, which were carried out at 37 °C for 10–30 min. Reactions were stopped by adding an equal volume of a mixture of 98.5% formamide, 0.025% bromphenol blue, and 0.025% xylene cyanol. Samples were fractionated by electrophoresis on 15 or 20% polyacrylamide gels containing 8 M urea, after which they were dried, visualized, and quantified using a Fuji BAS 2500 phosphorimaging device. Primer extension was calculated by dividing the amount of all extended primers by the sum of extended and non-extended primers. The extent of bypass was calculated by dividing the amount of bypass products by the amount of all extended primers. To qualitatively examine the specificity of primer extension by pol $\mu$, the reactions were carried out under similar conditions in the presence of a single dNTP at concentrations of 1, 10, and 100 $\mu$M. The efficiency of extension was calculated by dividing the amount of extended primers by the total amount of primers.

Steady-state Kinetic Analyses—Analysis of kinetic parameters for primer extension from the abasic site or deoxynucleotide incorporation opposite an undamaged nucleotide template was performed as follows.

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¶ Incumbent of The Maxwell Ellis Professorial Chair in Biomedical Research and to whom all correspondence should be addressed. Tel.: 972-8-934-3203; Fax: 972-8-934-4169; E-mail: zvi.livneh@weizmann.ac.il.

$^*$ The abbreviations used are: pol $\mu$, DNA polymerase $\mu$; NHEJ, non-homologous end joining.
Human pol μ (at 25 nM) was incubated with increasing concentrations of a single deoxynucleotide (1–2000 μM; 6–8 concentration points) and with 50 nM DNA substrate for 20 or 30 min under standard reaction conditions. Gel band intensities of the substrates and products were quantified as described above. The percentage of primer extended was duplicated by 1000 fmol and divided by the time of the reaction to give \( V_{obs} \) values. These values were plotted using the Lineweaver-Burk double-reciprocal plot of the Michaelis-Menten equation, namely 1/\( v \) = 1/\( V_{max} \) + \( K_m \) / (dNTP)\( V_{max} \). Apparent \( K_m \) and \( V_{max} \) steady-state parameters were obtained from the fit and used to calculate the frequency of deoxynucleotide incorporation (\( f_{inc} \)) using the equation
\[
\frac{V_{max}}{K_m} \times \frac{\text{incorrect nucleotide}}{\text{correct nucleotide}}.
\]
For each substrate a set of 3–5 experiments was carried out under conditions in which primer utilization was <25%.

RESULTS

Purified Pol μ Effectively Bypasses a Single or Two Tandem Abasic Site(s)—The ability of pol μ to replicate across DNA blocking lesions was assayed using primed oligonucleotides, each carrying a site-specific synthetic abasic site. Abasic sites are common lesions in DNA, formed both spontaneously and by DNA damaging agents such as ionizing radiation (13, 14). Abasic sites were shown to severely block polymerization by purified prokaryotic (e.g. Refs. 10, 11, 15–18) and eukaryotic DNA polymerases (12, 17, 19–22).

Fig. 2 shows standing start primer extension assays performed with purified pol μ, using two different primer-templates. When template AB1G, containing a synthetic abasic site was used, primer extension by pol μ was similar to that obtained in the absence of the lesion (Fig. 2A, compare lanes 2 and 5). In contrast, primer extension by pol I (Klenow fragment) was strongly inhibited on this DNA substrate (Fig. 2A lane 3), consistent with previous results (11). Similar results were obtained with another DNA substrate, AB2C (Fig. 1), in which the abasic site was located in a different sequence context (Fig. 2A, lanes 7–12). We have also analyzed the ability of pol μ to bypass two tandem abasic sites in a different sequence context by using template ABXX33 (Fig. 1). E. coli pol I (Klenow) was completely blocked by the two tandem abasic sites (Fig. 2B, lane 2). In contrast, pol μ extended the primer across the two tandem abasic sites, although at a lower efficiency than across a single abasic site (90 and 44% primer extension, re-
spectively; Fig. 2B, compare lanes 3 and 4). Most remarkably, pol \( \mu \) did not show any pause at the site of the lesions, and bypass per se was little affected (93% bypass of a single abasic site and 84% bypass of two tandem abasic sites; Fig. 2B). The decreased activity on the substrate with the two tandem abasic sites, as compared with the single lesion template, is therefore due to inhibition of synthesis initiation rather than inhibition of lesion bypass.

Pol \( \mu \) Uses Misalignment to Bypass Abasic Sites—To elucidate the mechanism by which pol \( \mu \) bypasses abasic sites, we examined the specificity of the nucleotide inserted opposite the abasic site. To this end, we performed standing start primer extension reactions with single dNTPs using template AB33A. As can be seen in Fig. 3a, when the template nucleotide next to the abasic site was an A, pol \( \mu \) incorporated primarily a dTMP residue. We assayed three additional variants of AB33A, each containing a different template nucleotide 5' to the abasic site (Figs. 1 and 3). As can be seen in Fig. 3, a–d, the specificity of incorporation by pol \( \mu \) was dependent on the template nucleotide next to the abasic site. In each case, the most frequent event was insertion of a nucleotide complementary to the template nucleotide 5' to the lesion. Pol \( \mu \) also inserts dGMP on these templates, although with lower efficiency (Fig. 3, a, b, and d). This is the nucleotide complementary to the template C located two nucleotides 5' to the abasic site. Taken together, these results suggest that pol \( \mu \) bypasses abasic sites by using a skipping mechanism in which the abasic site is “flipped out” and the polymerase replicates the next template nucleotide, similar to the bypass by pol \( \beta \) (20, 21). Consistent with this suggestion, pol \( \mu \) incorporated primarily dGMP on another template (AB2C), where a template C is located 5' to the lesion (Fig. 3e).

The same mechanism was probably used when pol \( \mu \) bypassed two tandem abasic sites, because mostly dGMP was incorporated by pol \( \mu \) on primed template ABXX33, where the first template nucleotide 5' to the two abasic sites is a C (Fig. 3f). In light of these results, the inhibition of synthesis initiation but not elongation by the two tandem abasic sites may be explained by the difficulty in skipping two abasic sites rather than only one.

Pol \( \mu \) Extends Primers Located Opposite an Abasic Site in a Sequence-independent Manner—The high bypass efficiency of pol \( \mu \) prompted us to analyze its ability to elongate primers located opposite the lesion. This was done using template AB1G, with a primer terminated as described under “Materials and Methods” with the indicated primer-templates and 50 nmol pol \( \mu \), E. coli pol IV, or pol I (KF, Klenow fragment) for 10 min at 37°C.
site the lesion (Fig. 4A, lanes 1, 3, 5, 7). This was somewhat surprising, because only the extension of C was expected to be effective if the polymerase uses a misalignment mechanism, as shown above. In contrast to pol μ, the E. coli DNA polymerase IV, which was shown to use template misalignment frequently (23, 24), could elongate only the primers terminated with C or A (Fig. 4B). These bases are complementary to the first or second template bases, respectively, 5’ to the abasic site, consistent with a mechanism of primer misalignment. Therefore, the ability of pol μ to extend effectively all four bases suggests that pol μ uses a mechanism other than primer misalignment when extending a nucleotide present opposite an abasic site.

Next we performed a qualitative analysis to determine the identity of the nucleotide extended by pol μ from specific abasic site:base mismatches. This was done using template AB33A primed with an oligonucleotide whose 3’-terminal nucleotide was located opposite the abasic site. Surprisingly, pol μ incorporated each one of the four dNMPs with apparently similar efficiencies (Fig. 5a). Similar results were obtained for substrates with a primer 3’-terminal A, C, G, and T (Fig. 5, a–d). This suggested a mode of DNA synthesis that is independent of the sequence of the template.

To quantify these results, we performed quantitative kinetic experiments in which we determined the $K_m$ and $V_{max}$ values for extension from abasic site:base mismatches in three different substrates, AB33A-0A, AB33G-0A, and AB33T-0C (Table I). As a control, we used AB33A with no lesion. As can be seen in Table I, when extending an abasic site:A mismatch on substrate AB33A0-A, pol μ essentially lost its ability to discriminate against insertion of the incorrect nucleotide. All four dNTPs were inserted with comparable efficiencies (within 2-fold from the correct nucleotide). A similar decrease in the ability to discriminate against insertion of the incorrect nucleotide was also observed with the other lesion-containing substrates that were used (Table I). In contrast, pol μ did show clear discrimination against insertion of the incorrect nucleotides when the control substrate without the lesion was used (Table I, AB33A control). To examine the specificity of extension in a different sequence context, a qualitative primer extension analysis was performed with primed template AB1G. As can be seen in Fig. 5, e–h, a similar picture was obtained;

![Embedded Image](Image 243x444 to 562x737)
Pol μ inserted all four dNMPs on each primer-template configuration. Only in the case of the 3’-terminal C in the primer strand was there preferential incorporation of dAMP, most likely due to misalignment, and template-directed incorporation opposite the next base (T). Still, even in this case, all other three dNTPs were incorporated by pol μ (Fig. 5, e–h).

The ability of pol μ to incorporate all four dNTPs when extending a primer terminus located opposite an abasic site may stem from local loss of template instruction, or from misalignment and instruction by template nucleotides at various positions 5’ to the lesion. To distinguish between these two possibilities, we performed a quantitative kinetic analysis of the specificity of extension in a substrate in which all 10 template nucleotides 5’ to the lesion were A (AB-(A-tail); Figs. 1 and 6A). This strongly biased one-nucleotide extensions to the insertion of dTMP, because any template-directed nucleotide incorporation, be it a direct extension or any misalignment event, is expected to yield dTMP incorporation on substrate AB-(A-tail). As can be seen in Fig. 6A, each of the four dNTPs was incorporated on this template. Moreover, multiple insertions were observed. Thus, with dATP as the only dNTP, extension by four nucleotides was observed, and a similar result was observed with dCTP as the only dNTP. Quite remarkably, when either dTTP or dGTP were used as the only dNTPs, there were multiple extension steps leading to a nascent DNA strand whose length exceeded the length of the template (Fig. 6). In the case of dTTP, this can be explained by template-instructed incorporation accompanied by primer slippage. However, in the case of dGTP, this indicates that long-range sequence-independent polymerization has occurred, as is discussed below. Primer extension analysis was performed also with another substrate, AB-(G-tail), which contains 10 G nucleotides 5’ to the abasic site (Figs. 1 and 6B). Results obtained with AB-(G-tail) were generally similar to those obtained with AB-(A-tail), except that the numbers of dNTP additions did not exceed the size of the G-tail (Fig. 6B).

We determined the kinetic parameters for the insertion of each of the four dNTPs on substrates AB-(A-tail) and AB-(G-tail) and on the control substrates without a lesion (Fig. 1 and Table II). As can be seen in Table II, all four nucleotides were inserted with similar efficiencies on the AB-(A-tail) substrate. In the case of the AB-(G-tail) substrate, dTTP and dGMP were incorporated best, and, most remarkably, the complementarily dCMP was inserted with the lowest efficiency, primarily due to a high $K_m$ value (Table II). Pol μ did discriminate against insertion of the wrong nucleotides in the control substrates without the lesion, although its fidelity was low, especially in the G-tailed substrate (Table II). These results indicate that pol μ can act as a template-dependent, sequence-independent DNA polymerase.

**DISCUSSION**

All known DNA polymerases, with the exception of one, function mainly as template-dependent DNA polymerases. The exception is terminal deoxynucleotidyl transferase, which adds nucleotides to a 3’-terminus of a primer in the absence of a template (25). The REV1 protein, which is a member of the Y family of DNA polymerases, was initially thought to be a dCMP transferase (26, 27). However, subsequent studies showed that it is a G template-specific DNA polymerase (28–30). The results presented above show that, given a primer terminus opposite an abasic site, pol μ adds each of the four dNTPs with no obvious preference, regardless of the sequence of the DNA template. This is, to the best of our knowledge, the first example of a DNA polymerase that is basically template-dependent but can act in a mode that is not-instructed by the sequence of the template. It is noteworthy that this nucleotidyl transferase activity occurs in the context of a primer-template, suggesting that it is a template-dependent dNMP transferase activity, unlike terminal deoxynucleotidyltransferase, which has a template-independent dNMP transferase activity. Interestingly, the transferase activity of pol μ seems to be activated only at
Reactions were carried out as described under “Material and Methods” with 50 nM primer-templates, 25 nM pol μ, for 20–30 min at 37 °C. The fidelity of nucleotide incorporation is indicated by the finc values, calculated as ($V_{\text{max}}/K_m$)$_{\text{corrected}}$/$V_{\text{max}}/K_m$.

| Substrate | $V_{\text{max}}$ | $K_m$ | $V_{\text{max}}/K_m$ | finc |
|-----------|-----------------|-------|----------------------|------|
| AB-(A-tail) dNTP | | | | |
| 5’GCTCA ↓ 3’CCAGA/A$_{10}$ | 4 ± 0.3 | 40 ± 4 | 0.10 | 1 |
| dATP | 11 ± 3 | 117 ± 27 | 0.09 | 0.8 |
| dGTP | 2 ± 0.1 | 30 ± 9 | 0.07 | 0.6 |
| dTTP | 8 ± 0.8 | 76 ± 7 | 0.11 | 1 |
| Cont-(A-tail) dNTP | | | | |
| 5’GCTCA ↓ 3’CCAGA/A$_{10}$ | 0.3 ± 0.07 | 150 ± 113 | 2 × 10$^{-3}$ | 4.6 × 10$^{-3}$ |
| dATP | 0.6 ± 0.2 | 215 ± 49 | 2.8 × 10$^{-3}$ | 5.8 × 10$^{-3}$ |
| dGTP | ND* | ND | ND | ND |
| dTTP | 12 ± 1 | 25 ± 6 | 0.48 | 1 |
| AB-(G-tail) dNTP | | | | |
| 5’GCTCA ↓ 3’CCAGG/G$_{10}$ | 15 ± 4 | 78 ± 13 | 0.19 | 1.6 |
| dATP | 25 ± 4 | 202 ± 49 | 0.12 | 1 |
| dGTP | 11 ± 1 | 15 ± 1 | 0.73 | 6 |
| dTTP | 16 ± 2 | 10 ± 1.5 | 1.6 | 13.3 |
| Cont-(G-tail) dNTP | | | | |
| 5’GCTCA ↓ 3’CCAGG/G$_{10}$ | 0.5 ± 0.2 | 500 ± 132 | 1 × 10$^{-3}$ | 2.3 × 10$^{-3}$ |
| dATP | 20 ± 4 | 46 ± 11 | 0.43 | 1 |
| dGTP | 1.6 ± 0.4 | 46 ± 3 | 0.03 | 0.07 |
| dTTP | 1 ± 0.8 | 83 ± 8 | 0.01 | 0.02 |

* ND, not determined.

Although the DNA polymerases of the Y family are specialized for lesion bypass, they are not the only ones capable of replicating across DNA lesions. For example, even high-fidelity DNA polymerases can bypass lesions aided by their processivity clamp (19, 21, 32, 33), and this may also occur in vivo (34, 35). Our results clearly show that pol μ bypasses abasic sites by using primarily a misalignment mechanism in which the abasic site is skipped-over, leading to a minus one deletion at the site of the lesion (data not shown). This is consistent with the tendency of pol μ to form frameshifts on undamaged DNA (6). The same mechanism is used by pol β (20), another member of the X family of DNA polymerases, for bypassing the same lesion. What is remarkable, though, is the very high efficiency of lesion bypass across the abasic site by pol μ. There is little pausing at the abasic site or even at the two tandem abasic sites, indicating bypass at a catalytic efficiency comparable with that of undamaged DNA. Nonetheless, bypass by pol μ creates a −1 deletion (31), which is different from the insertion specificity opposite the abasic site in vivo (35). Our results are in agreement with recent reports on the ability of pol μ to bypass a variety of DNA lesions (31, 36).
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