Error-prone bypass of certain DNA lesions by the human DNA polymerase κ

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The Escherichia coli protein DinB is a newly identified error-prone DNA polymerase. Recently, a human homolog of DinB was identified and named DINB1. We report that the DINB1 gene encodes a DNA polymerase (designated polκ), which incorporates mismatched bases on a nondamaged template with a high frequency. Moreover, polκ bypasses an abasic site and N-2-acetylaminofluorene (AAF)-adduct in an error-prone manner but does not bypass a cis–syn or [6-4] thymine–thymine dimer or a cisplatin–adduct. Therefore, our results implicate an important role for polκ in the mutagenic bypass of certain types of DNA lesions.

Received March 20, 2000; revised version accepted May 18, 2000.

Accurate replication of chromosomal DNAs requires DNA polymerases with high processivity and fidelity [Kornberg and Baker 1992]. The high fidelity primarily depends on the proofreading 3′-to-5′ exonuclease activities of replicative DNA polymerases to remove erroneously incorporated nucleotides. Most, if not all, living organisms are endowed with another class of DNA polymerase that lacks this proofreading activity and is able to replicate past damaged bases, but at the increased risk of causing mutations [Friedberg et al. 1995; Friedberg and Gerlach 1999; Johnson et al. 1999d; Woodgate 1999]. The Escherichia coli UmuD′,C complex has been recently shown to be one of such enzymes and designated pol V [Reuven et al. 1999; Tang et al. 1999]. Saccharomyces cerevisiae has at least three different enzymes for translesion synthesis. Among them, Rev1 incorporates dCMP exclusively opposite an abasic site [Nelson et al. 1996a]. Rev3 and Rev7 proteins form DNA polymerase ζ, which is able to bypass a cis–syn thymine–thymine (T-T) dimer [Nelson et al. 1996b]. Rad30 is another DNA polymerase in that can efficiently bypass cis–syn T-T dimers [Johnson et al. 1999b]. Rev1 and Rad30 share some homologies with UmuC, whereas Rev3, the catalytic subunit of pol ζ is similar to replicative DNA polymerases. Recently, a human homolog of Rev3 was identified and shown to be involved in UV-induced mutagenesis [Gibbs et al. 1998]. Furthermore, the gene responsible for the human disease xeroderma pigmentosum variant (XP-V) was shown to code for a Rad30 homolog that bypasses a cis–syn T-T dimer, but not a [6-4] T-T dimer [Johnson et al. 1999a; Masutani et al. 1999a,b]. The S. cerevisiae Rad30 and the human XPV enzymes are considered to be error-free because they insert two dAMPs opposite a cis–syn T-T dimer in vitro and the absence of their activities leads to enhanced levels of mutagenesis in vivo [Johnson et al. 1999a,b,c; Masutani et al. 1999a,b].

E. coli has another DNA polymerase (DinB, pol IV) [Wagner et al. 1999] with some similarity in amino-acid sequence to UmuC and its homologs [Ohmori et al. 1995; Kim et al. 1997]. Overexpression of dinB resulted in a dramatic increase in frameshift mutations in F lac plasmids without any exogenous DNA-damaging treatment [Kim et al. 1997]. Recently, mouse and human homologs of DinB were identified, and the genes were designated Dinb1 and DINB1, respectively [Gerlach et al. 1999; Ogi et al. 1999]. Furthermore, it was shown that transient expression of the mouse Dinb1-cDNA in cultured cells caused a nearly 10-fold increase in the incidence of 6-thioguanine resistance mutations, in which one-third were frameshift mutations and most of the rest were base-substitution mutations [Ogi et al. 1999]. Therefore, the action of the mammalian DinB homologs seemed to be error-prone, similar to the E. coli DinB. It remained unknown, however, whether mammalian DinB homologs possess any DNA polymerase activity, and if so, whether they could facilitate bypass of damaged DNA. In this paper, we show that a truncated form of the human DINB1 [hDINB1] protein does exhibit DNA polymerase activity that allows for the bypass of certain DNA lesions in an error-prone manner.

Results and Discussion

The hDINB1 protein comprises three portions [NT, HDB, and CT regions; see Fig. 1A], among which the NT+HDB and CT regions show 88% and 60% identity, respectively, with the corresponding region of the mouse homolog [Ogi et al. 1999]. The HDB region contains all of the multiple motifs conserved among the DinB homologs, suggesting that the HDB region should be essential for a DNA polymerase activity and the CT region might be dispensable for catalytic activity. In support of this idea, the XPV protein [human polν], which contains the common five motifs shared among the UmuC/DinB family proteins in the amino-terminal half, exhibits enzyme activity even in the absence of a portion of its carboxyl terminus [Masutani et al. 1999a,b]. Our attempt to overproduce the intact size of hDINB1 with a His–Tag sequence at the carboxyl terminus by using a Baculovirus system resulted in a very low yield, partly attribut-

[Key Words: DINB1; polκ; abasic site; AAF; mutation; sequence context]
Proteins (New England Biolabs) and visualized by CBB staining. (C) SDS-PAGE analysis of purified proteins. The purified proteins (350 ng each) were analyzed by electrophoresis on a 10% SDS-PAGE with marker proteins (New England Biolabs) and visualized by CBB staining. (C) DNA polymerase activity. Four different amounts of DINB1C and DINB1C-D198N (0.04, 0.4, 4, and 40 nM from left to right) were added in the reaction mixture. After incubation at 37°C for 15 min, the reaction products were analyzed by electrophoresis on 20% polyacrylamide/7M urea sequencing gel followed by autoradiography.

Next, we investigated whether polkC could bypass various DNA lesions. As shown in Figure 3A, polkC did not bypass a cis–syn or [6–4] T–T dimer. In contrast, polkC bypassed a synthetic abasic site that is very similar to, but more stable than, the natural abasic site (Shibutani et al. 1997). Even at an ~1:10 molar ratio of dNTP, no degradation of the primer was observed, indicating that the preparation was virtually free from intrinsic or contaminating exonuclease (data not shown). For qualitative analysis on the fidelity of polkC on a nondamaged DNA template, we measured incorporation of a mismatched base at the end of various primers in the presence of a single dNTP. As shown in Figure 2, B–D, polkC selectively incorporated the complementary bases opposite dA, dC, and dG in the template; however, it reproducibly showed high levels of misincorporation opposite T [Fig. 2A,E]. Note that the single base change from dC to T is the only difference in the sequence between the templates used in Figure 2, D and E. At the present time, we have no clear explanation for why polkC exhibits such high levels of misincorporation, especially of C, opposite nondamaged T.

Figure 2. Fidelity of polkC on nondamaged DNA template. The 30mer with the indicated sequence [A–D] or with the G-to-T substitution [E] was annealed with a 5′-labeled primer of different length. The primer-template (40 nM) was incubated with 0.04 nM of polk in the absence of dNTP [0] or in the presence of a single dNTP (A, T, G, and C) or all of the four dNTPs [4]. The reaction products were analyzed, as described in the legends to Fig. 1.
enzyme versus the primer-template (the rightmost lane in Fig. 3A), polkΔC showed a significant level of bypass past the lesion although it stopped after incorporating one nucleotide opposite the abasic site at an equivalent proportion. To explore which residue could be incorporated opposite abasic site, we employed two different templates containing T (the AP-T template) or dA (the AP-A template) immediately 5' to the abasic site. In both cases, when incubated with a single dNTP, polkΔC incorporated dAMP most preferentially and to a lesser extent dCMP opposite the abasic site (Fig. 3B,C). Therefore, polkΔC seemed to be similar to many other enzymes preferentially incorporating dAMP opposite abasic sites (Efrati et al. 1997). In the presence of four dNTPs, however, polkΔC was found to generate a −1 deletion during the bypass of the abasic site, which was sequence dependent. The size of the major replication product generated by polkΔC with the AP-T template was shorter by one nucleotide than the product generated with the control nondamaged template [Fig. 3A]. The same result was obtained when Klenow fragment was added after the normal reaction by polkΔC, to complete elongation to the end of the template [Fig. 3D]. On the other hand, polkΔC generated predominantly the full-size product with the AP-A template. For the reaction, an equal amount of polkΔC (40 nM) was added to the reaction mixture, because the efficiency of elongation past the lesion in the AP-A template was consistently much lower than in the AP-T template [Fig. 3B,C]. Taken together, these results suggest that polkΔC preferentially incorporates dAMP opposite the synthetic abasic site, but a realignment may occur before the nonprocessive polkΔC enzyme inserts another residue at the da-abasic mismatched terminus [see Fig. 3E]. In the case of the AP-T template, the dA residue incorporated opposite the abasic site can form base-pairing with the T residue 5' to the abasic lesion in the template, placing the abasic lesion in an extrahelical position. In such a configuration, dGMP can be incorporated opposite the next dC in the template in the presence of four dNTPs, thereby stabilizing the misaligned structure and eventually generating −1 deletion. If dATP is the only available substrate, polkΔC adds dA opposite the T residue 5' to the abasic site at the da-abasic mismatched terminus (see lane A in Fig. 3B). With the AP-A template, no slippage is possible and polkΔC has no choice other than to extend the mismatched dA primer. In the template, polkΔC bypassed the abasic site with a reduced frequency and mostly stopped after incorporating one nucleotide opposite the abasic site [Fig. 3C]. Furthermore, we found that polkΔC was able to bypass an N-2-acetylaminofluorene [AAF]-modified guanine (Fig. 4A), but it did not bypass a cis-diaminedichloroplatinum [cisplatin]-adducted G-G [Fig. 4B]. To explore which residue was incorporated opposite dG–AAF, we performed similar experiments as described above, by employing two templates which differed from each other only at the two nucleotides 5' to the AAF-adduct [3'-dG- AAF] AT-5' in the AAF-A template and 3'-dG-AAF] TA-5' in the AAF-T template. When incubated in the presence of a single dNTP, the primer was extended most effectively in the presence of dTTP in both cases [Fig. 4C,D]. The size of the major replication products generated with both templates after supplementing with Klenow enzyme was the same length as that generated with the nondamaged template [Fig. 4E]. This result indicates that polkΔC most likely bypassed the dG–AAF adduct without skipping over the lesion. Although it remains to be clarified why polkΔC incorporates preferentially T opposite dG–AAF in the two different templates used here, the results shown in Figure 4, C and E, indicate that further elongation past the AAF-adduct was observed with the correct base, that is, T in the AAF-A template or A in the AAF-T template. This result implies that polkΔC retains the ability to select and add the correct base at the mismatched terminus between dG–AAF and T or A.

As described above, we have shown that polkΔC can bypass two different DNA lesions, a synthetic abasic site and an AAF–adduct, in an error-prone manner depending on the context of the neighboring sequence. PolkΔC was unable, however, to bypass DNA lesions spanning two adjacent nucleotides such as the cis–syn or [6-4] T-T dimer or the cisplatin–adduct. High fidelity of replicative DNA polymerases depends on proofreading activity and strong base-selection, that is, adding only the base
complementary to a template base at the perfectly matched primer terminus. Efficient translesion synthesis by a given DNA polymerase becomes possible only when both of the two properties are alleviated to some extent. Consistent with this, polkΔC showed a significant level of misincorporation opposite nondamaged T (Fig. 2A,E), elongation past the abasic site with a probable misalignment (Fig. 3), elongation at the mismatched termini between dG–AAF, and T or A (Fig. 4C,D). Our results demonstrate that a truncated form of polk deleting the carboxy-terminal 310 amino acids is active as a DNA polymerase capable of continuing DNA synthesis past certain DNA lesions, implying that the carboxy-terminal region is not required for the catalytic activity per se. The carboxy-terminal region containing two copies of Zinc-cluster, which is conserved in eukaryotic DinB homologs (Gerlach et al. 1999; Johnson et al. 1999d), may be involved in increasing processivity through DNA binding by the Zinc-clusters and/or interacting with other protein[s] within the cells. It is intriguing as to how polk (or any other enzyme for translesion synthesis for that fact) is recruited in vivo to the site where a replicative polymerase is stalled by the presence of a blocking lesion. In any case, because of the low processivity of such enzymes involved in translesion synthesis, error-prone synthesis is probably restricted to a very short region following the lesion, after which a replicative DNA polymerase should take over.

Our results verify the difference between polk and human polη in some crucial respects regarding translesion synthesis. Whereas polk carries out error-prone bypass of certain DNA lesions, polη appears to contribute to the general error-free bypass of various DNA lesions. In fact, when the same templates examined in this work were used, polη bypassed not only *cis-syn* T-T dimer by incorporating two As [Masutani et al. 1999a] but also the AAF-modified G and cisplatin-croslinked GG, although at lowered efficiencies compared with bypass of *cis-syn* T-T dimer, by incorporating preferentially dCMP opposite the lesions [Masutani et al. 2000]. Furthermore, polη bypassed the abasic site in the AP-A template by incorporating dAMP or dGMP without making −1 deletion [Masutani et al. 2000]. XPV patients are predisposed to sunlight-induced skin cancer, probably because an error-prone pathway is used, instead of the polη-dependent error-free pathway, to bypass UV-induced DNA lesions (Cordonnier and Fuchs 1999; Masutani et al. 1999a). It seems unlikely that polk is involved in the enhanced mutagenesis in XPV cells, since polkΔC was unable to bypass a *cis-syn* or (6-4) T-T dimer (Fig. 3A). XPV cells are also generally defective in bypassing an AAF–adduct, while still retaining a minor error-prone pathway (Cordonnier et al. 1999). Whether polk is involved in this minor error-prone pathway needs to be experimentally examined. Our finding that polkΔC incorporated most preferentially T opposite dG–AAF in the two different templates with either A or T 5′ to the lesion is unexpected, but not unprecedented because dG–AAF is known to produce G-to-A transitions, although to a much lesser degree compared with G-to-T transversions or deletion formations, in simian kidney [COS-7] cells (Shibutani et al. 1998).

Finally, we should emphasize our finding that polkΔC is able to bypass abasic sites with variable efficiencies and in an error-prone manner that is heavily dependent on the sequence context. Very recently, Johnson et al. (2000) reported that the human *DINB1* gene product (they designated it polδ instead of polk) was unable to bypass an abasic site under the conditions they used. The difference between their result and ours may be attributable to the fact that they examined a single species of the template with a low concentration of the enzyme (0.5 nM against 10 nM of DNA substrate). As shown in Figure 3A, polkΔC did not bypass the abasic site in the AP-T template at the enzyme/template ratio of 1:100, although the enzyme showed a substantial extent of bypass at the ratio of 1:10. Abasic sites are the most common lesions in DNA within cells, and are generated by spontaneous hydrolysis of the N-glycoside bond [estimated 2,000–10,000 per cell per day] as well as intermediates during the course of repairing base-damage generated by carcinogenic agents and ionizing radiation (Lindahl 1993). The mRNAs coding for polk are most highly expressed in testes in both humans and mice, although they are also expressed at lower levels in many other
tissues [Gerlach et al. 1999; Ogi et al. 1999]. Taken together, the results described above implicate polk in carcinogenesis in somatic cells and causing higher mutation rates in males than in females [Crow 1997].

Materials and methods

Protein purification

A truncated form of hDINB1 [DINB1ΔC] and a corresponding mutant containing an amino acid change of aspartic acid to asparagine at residue 198, both with a 6xHis-tag attached at the carboxyl terminus, were overproduced using the BAC-to-BAC Baculovirus Expression System kit (GIBCO BRL). Briefly, derivatives of the vector plasmid FASTBAC1 (GIBCO BRL) containing the corresponding DNA sequence were constructed via several steps of PCR amplification and subcloning from a plasmid that contained the full-length DINB1 cDNA sequence. The plasmids were used to transform the E. coli strain DH10BAC to spontaneously generate recombinant bacmids carrying the respective protein-coding region in a Baculovirus sequence. High-molecular-weight DNAs containing the recombinant bacmid were prepared and used to transfect the SF9 cells.

The SF9 cells infected with the recombinant Baculovirus were lysed in Lysis buffer [20 mM sodium phosphate (pH 7.4), 0.3 mM NaCl, 1% Nonidet-P 40] on ice with occasional stirring. The lysate was centrifuged at 50,000 rpm in Beckman 70Ti rotor for 1 hr and the supernatant containing the truncated DINB1 protein was supplemented with imidazole at 50,000 rpm in Beckman 70Ti rotor for 1 hr and the supernatant containing the truncated DINB1 protein was supplemented with imidazole at the final concentration of 50 mM, and applied to 1 ml of a Ni-NTA silica resin (Qiagen) packed in an HR5/5 connected to an FPLC system. The column was washed with A buffer [20 mM sodium phosphate (pH7.4), 0.3 mM NaCl, 10% glycerol] containing 50 mM imidazole and eluted in a gradient of 50–500 mM imidazole in A buffer. The truncated DINB1 protein was eluted at –180 µM imidazole.

DNA polymerase assay

The 30mer with the sequence 5′-CTCTCAGCATCTTCATCATA-CAGTCAGTG-3′ was used as a nondamaged template. The same 30mer containing a cys-syn dimer (CPD) or [6-4] photoproduct at the underlined site was chemically synthesized as described previously [Murata et al. 1999; Iwai et al. 1996]. The two 30mers containing tetrahydrofuran instead of natural abasic site, AP-A (5′-CTCTCAGCATCTTCATCATA-CAGTCAGTG-3′) and AP-T (5′-CTCTCAGCATCTTCATCATA-CAGTCAGTG-3′), in which X denotes abasic site, were synthesized as CAGTCAGTG-3′–32P] ATP and annealed with template at a molar ratio of 1:1.

Standard reactions (10 µl) contained 40 mM Tris-HCl (pH8.0), 5 mM MgCl2, 100 µM each of four dNTPs, 10 mM DTT, 250 µg/ml BSA, 60 mM KCl, 2.5% glycerol, 40 nM primer-template, and an indicated amount of enzyme. After incubation at 37°C for 15 min, reactions were terminated by the addition of 10 µl of formamide followed by boiling. The products were subjected to 20% polyacrylamide/7 M urea gel electrophoresis followed by autoradiography.

Acknowledgments

We thank Dr. R. Woodgate at The National Institutes of Health for greatly improving the manuscript and Dr. E. Bruford at the HUGO Nomenclature Committee for advice in naming the hDINB1 protein. We also thank the two anonymous referees for careful reading of the manuscript and constructive advice. This work was supported in part by Grants-In-Aid for Scientific Research of priority area from the Ministry of Education, Culture, Sports, and Science of Japan.

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Genes Dev. 2000, 14:
Access the most recent version at doi:10.1101/gad.14.13.1589

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