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dnaX36 Mutator of *Escherichia coli*: Effects of the τ Subunit of the DNA Polymerase III Holoenzyme on Chromosomal DNA Replication Fidelity[▽]

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The *Escherichia coli dnaX36* mutant displays a mutator effect, reflecting a fidelity function of the *dnaX*-encoded τ subunit of the DNA polymerase III (Pol III) holoenzyme. We have shown that this fidelity function (i) applies to both leading- and lagging-strand synthesis, (ii) is independent of Pol IV, and (iii) is limited by Pol II.

The mechanisms by which organisms achieve a high accuracy of DNA replication are of ongoing interest. Replication of the chromosome of the bacterium *Escherichia coli* is performed by the DNA polymerase III (Pol III) holoenzyme (HE). HE is composed of 17 subunits (10 distinct), with an overall composition $(\alpha\epsilon\theta)_2\beta_4\tau_2\gamma\delta\delta'\chi\psi$ (27). It contains two $(\alpha\epsilon\theta)$ polymerase core assemblies, one for the leading strand and one for the lagging strand. The α subunit is the DNA polymerase, ε is the $3' \rightarrow 5'$ proofreading exonuclease, and θ is an ε-stabilizing factor (2, 17, 34). Within HE, a central role is played by the τ subunit (τ_2), which has several important functions, including connecting the two polymerases, enabling coupled leading- and lagging-strand synthesis. For the fidelity of replication, most of the focus has been on the DNA polymerase III core, notably the polymerase and the proofreading subunit (26, 28, 29). However, it is clear that overall chromosomal fidelity is not simply a function of polymerase fidelity but also involves activities of other HE subunits—as evidenced by mutator effects associated with defects in such subunits (24, 30, 32)—and the participation of accessory DNA polymerases (1, 8, 9, 12–14, 23, 35), of which *E. coli* has four (Pol I, II, IV, and V).

The present study is concerned with the fidelity role of the central τ subunit of HE, encoded by the *dnaX* gene, which also encodes the γ subunit (6). τ is the full-length product of the gene (643 amino acids), while the γ subunit is an early termination product (residues 1 to 430). Since τ and γ share the N-terminal protein sequence (domains I, II, and III), they share certain functions, such as the loading and unloading of the β-processivity clamps (27). However, the two additional domains (IV and V) that are present in τ permit it to perform certain unique functions. Specifically, domain IV contains the site of interaction with the DnaB helicase (10), which positively regulates the speed of the replication fork (4). Domain V contains the τ-α interaction site that enables HE to be dimeric (11). Domain V also controls the cycling of the lagging-strand

polymerase, as it mediates the release of the Pol III core from its β processivity clamp upon completion of Okazaki fragments (20, 21). Thus, τ is an important control element within HE that can influence polymerase behavior, and this may extend to HE fidelity.

A fidelity role for the τ subunit was proposed based on observations of a distinct mutator activity for certain *dnaX* mutants (30). In particular, *dnaX36* was informative since its defect (E601K) resides in domain V and hence only affects τ. Presumably, in the *dnaX36* mutant, the τ-α interaction is altered, leading to the mutator effect. An additional series of *dnaX* mutators was also isolated, each carrying an amino acid substitution in domain V critical for interaction with the α subunit (15, 30, 33). Interestingly, they all share a unique mutational specificity: enhanced transversion base substitutions and (−1) frameshifts (in nonrun sequences) (30). To explain these observations, we suggested that the role of τ in fidelity is indirect. In this model, τ does not affect the intrinsic accuracy (insertion fidelity) of the α subunit but instead is involved in facilitating the subsequent (presumably error-free) processing of terminal mismatches created by Pol III.

***dnaX36* mutator effects during chromosomal replication.** Our previous studies on the *dnaX36* mutator effect were performed with *lac* mutational targets located on an F′ episome (12). While F′ replication is performed by Pol III HE, this type of replication may differ in important aspects from chromosomal replication. Presently, we have analyzed the effect of *dnaX36* specifically on chromosomal DNA, using a system that also allows assessment of differential leading- and lagging-strand effects. We used a set of four different *lacZ* missense alleles that permit reversion to *lac*+ by a defined base-pair substitution ($G \cdot C \rightarrow A \cdot T$, $G \cdot C \rightarrow T \cdot A$, $A \cdot T \rightarrow T \cdot A$, or $A \cdot T \rightarrow G \cdot C$, respectively) (3). For each *lac* allele, two strains that differ only in the orientation of the *lac* operon are used. Comparison of the *lac* mutant frequencies for the two orientations allows assessment of differential leading- and lagging-strand effects (5). The experiments are performed with strains defective in *mutHLS* postreplicative mismatch repair, facilitating interpretation of mutation rates in terms of replication error rates (1, 5, 18, 22, 23).

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TABLE 1. Mutability of *dnaX36* strains as function of chromosomal *lac* orientation[a]

lac reversion	Expt	*lac* orientation (strand)	No. of *lac*+ mutants per 10[8] cells		Mutator effect (fold)
			dnaX+	*dnaX36*	
G · C → A · T	1	L (leading)	68	106	1.6
		R (lagging)	20	50	2.5
	2	L (leading)	73	215	2.9
		R (lagging)	19	76	4.0
G · C → T · A	1	L (leading)	1.1	11	10
		R (lagging)	0.6	16	27
	2	L (leading)	0.7	8.0	11
		R (lagging)	0.4	14	35
A · T → T · A	1	L (leading)	1.1	2.2	2.0
		R (lagging)	0.7	3.3	4.7
	2	L (leading)	1.3	2.0	1.5
		R (lagging)	0.7	2.7	3.9
A · T → G · C	1	L (lagging)	3.0	13	4.3
		R (leading)	25	29	1.2
	2	L (lagging)	5.6	14	2.5
		R (leading)	20	25	1.3

[a] Each mutant frequency entry is based on 30 independent cultures comprising three independent *lacZ* chromosomal integrants for each orientation. The strains are the *lac*-containing derivatives of MC4100 described previously (5), into which the *dnaX36* allele was introduced by P1 transduction using linkage with the *zba-2321*::mini-Tn*10cam* transposon (12). All strains are also mismatch repair deficient (*mutL*). The assignment of leading- or lagging-strand events is based on the *lac* orientation (L or R) and the assumed mispairings that underlie each of the indicated base-pair substitutions, i.e., G · T, T · C, T · T, and T · G for the G · C → A · T, G · C → T · A, A · T → T · A, and A · T → G · C substitutions, respectively, as previously described (5).

Table 1 shows the results of two independent experiments. "L" and "R" indicate the strand in which the underlying mutational event is assumed to take place (see footnote *a*) (5). The *dnaX36* mutator effect is 1.6- to 4.0-fold for the *lac* G · C → A · T transition depending on the orientation and experiment, 10- to 35-fold for the G · C → A · T transversion, 1.5- to 4.7-fold for the A · T → T · A transversion, and 1.2- to 4.3-fold for the A · T → G · C transition. Overall, we conclude that the *dnaX36* mutator effect is readily observable on the *E. coli* chromosome and that both strands are affected, although not to the same extent.

Consistent with previous observations (1, 5, 18, 22, 23), the mutant frequencies for each of the *lac* alleles in control (*dnaX*+) strains are consistently higher for leading-strand replication than for lagging-strand replication. This persistent bias is the basis for our contention that on the *E. coli* chromosome, lagging-strand replication is more accurate. The mechanism underlying the higher fidelity for lagging-strand replication is not known but may be related to the more efficient editing of polymerase errors in this strand (1, 5).

For the *dnaX36* strain, it is clear that in each case the mutator effect is stronger for the lagging-strand events. For example, for the *lac* G · C → T · A allele, the mutator effect is 10- or 11-fold on the leading strand and 27- or 35-fold on the lagging strand. In fact, for this allele, the strand bias is inverted: the lagging strand now mutates at a higher level than the leading strand. Likewise, an inversion of the strand bias is seen for the *lac* A · T → T · A allele. For the two transitions,

G · C → A · T and A · T → G · C, no inversion is seen, but the difference between the two strands is significantly diminished. Two conclusions are drawn from these experiments. First, in the absence of proper τ function, fidelity suffers in both strands, indicating τ promotes high fidelity in both strands. Second, the fidelity role of τ is quantitatively more important in the lagging strand than in the leading strand.

Role of accessory DNA polymerases. Recent studies have shown that accessory DNA polymerases may also participate, at least occasionally, in chromosomal DNA synthesis. Obviously, DNA polymerase I plays an important role in lagging-strand replication, clearing and filling the Okazaki fragment gaps. Other DNA polymerases (Pol II, IV, and V) may occasionally gain access to the replication point and displace/replace Pol III, most obviously when the progress of Pol III HE is somehow blocked, either at DNA damage sites or, as we have proposed, at persistent terminal mismatches (1, 12, 18, 23). In the experiments shown in Fig. 1, we investigated the roles of Pol II and Pol IV. The role of Pol IV is probed by deleting the *dinB* gene, which encodes Pol IV, while the role of Pol II is investigated by using either a deletion allele, Δ*polB*, or a proofreading (exonuclease) defective allele, *polBex1* (7). The *polBex1* allele (D155A, E157A) (7) is particularly useful because this allele may convert a normally error-free contribution into an error-prone contribution that may be revealed by an increase in the mutation rate (1, 7, 12, 31).

Pol IV is normally present in wild-type cells at the relatively high concentration of ~250 molecules per cell (16). Nevertheless, studies have indicated that under those conditions, Pol IV does not affect the chromosomal error rate (19, 36). Our present results (Fig. 1) confirm this (compare *dnaX*+ Δ*dinB* results to those for *dnaX*+). In the *dnaX36* background, the loss of Pol IV (*dinB*) has only some very small effects. No significant effect is seen for the G · C → T · A allele in the leading-strand (L) orientation or for both orientations of the A · T → T · A allele. An approximately 30% reduction is observed for the G · C → T · A transversion in the lagging-strand orientation (11 × 10⁻⁸ versus 15 × 10⁻⁸) (Fig. 1). This reduction, while modest, has been observed repeatedly in several experiments (data not shown) and thus likely represents a real effect. We conclude that the *dnaX36* mutator effect is largely independent of the error-prone involvement of Pol IV. These results differ from those obtained with the F′ system, where a large fraction of *dnaX36*-mediated mutations proved Pol IV dependent (12). Presumably this reflects the fact that F′ *pro lac*-containing strains contain an extra copy of the *dinB* gene and possess some 4-fold-elevated levels of Pol IV (16).

A lack of Pol II (Δ*polB*) does not affect mutagenesis in wild-type (*dnaX*+) cells (Fig. 1), consistent with previous reports (1), but it modestly increases the *dnaX36* mutator effect for both *lac* alleles. The effect is most pronounced for the G · C → T · A allele: about 1.7-fold for the leading-strand orientation (18 × 10⁻⁸ for *dnaX36* versus 11 × 10⁻⁸ for *dnaX36* Δ*polB*) and 3-fold for the lagging-strand orientation (14 × 10⁻⁸ versus 46 × 10⁻⁸) (Fig. 1). These results indicate that Pol II plays a role in preventing mutations in *dnaX36* strains and that this role may be more important in lagging-strand replication. Interestingly, an additional loss of Pol IV (*dnaX36* Δ*polB* Δ*dinB* strain) leads to a reduction
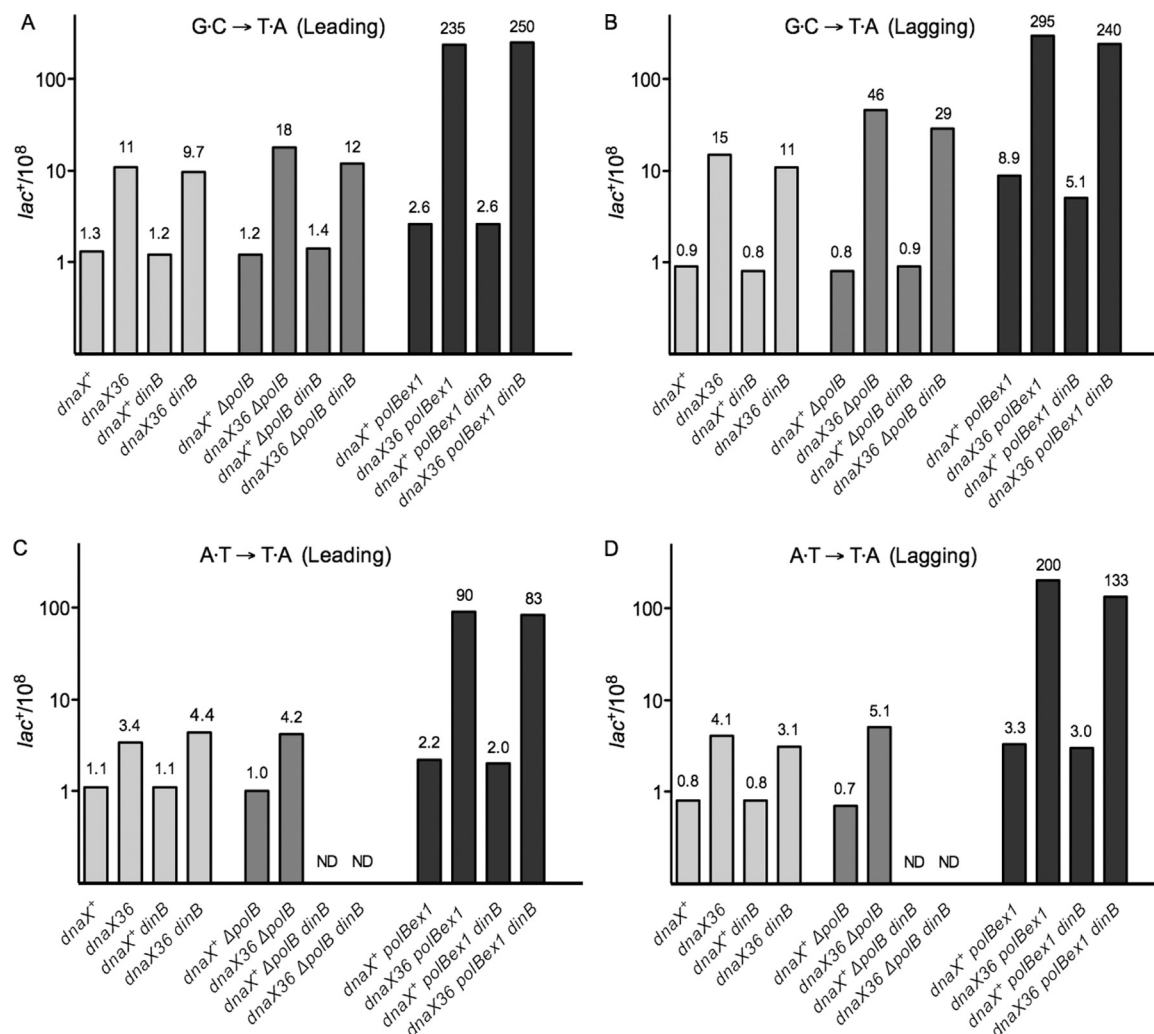
FIG. 1. Effect of Pol IV (Δ*dinB*) and Pol II (Δ*polB* and *polBex1*) on *dnaX36* mutator activity. All strains are also mismatch repair deficient (*mutL*). Mutant frequencies were determined as described previously (1, 12). The strains used are *lac*-containing derivatives of MC4100 (5) into which the indicated *dnaX*, *dinB*, and *polB* alleles were introduced by P1 transduction as described previously (1, 5, 12). Each entry is based on at least 30 independent cultures. Average mutant frequencies with standard errors (SE) were determined using the statistical software program Prism (GraphPad). (A) Mutant frequencies for *lac* $G \cdot C \rightarrow T \cdot A$ transversions in the L (leading-strand) orientation. The mutant frequencies $\pm$ SE values were as follows: *dnaX*[+], 1.3 ± 0.3; *dnaX36*, 11 ± 0.5; *dnaX*[+] *dinB*, 1.2 ± 0.1; *dnaX36 dinB*, 9.7 ± 1; *dnaX*[+] Δ*polB*, 1.2 ± 0.2; *dnaX36* Δ*polB*, 18 ± 3; *dnaX*[+] Δ*polB dinB*, 1.4 ± 0.2; *dnaX36* Δ*polB dinB*, 12 ± 3; *dnaX*[+] *polBex1*, 2.6 ± 0.3; *dnaX36 polBex1*, 235 ± 19; *dnaX*[+] *polBex1 dinB*, 2.6 ± 0.4; *dnaX36 polBex1 dinB*, 250 ± 9. (B) Mutant frequencies for *lac* $G \cdot C \rightarrow T \cdot A$ transversions in the R (lagging-strand) orientation. The mutant frequencies $\pm$ SE values were as follows: *dnaX*[+], 0.9 ± 0.2; *dnaX36*, 15 ± 1.2; *dnaX*[+] *dinB*, 0.8 ± 0.2; *dnaX36 dinB*, 11 ± 0.7; *dnaX*[+] Δ*polB*, 0.8 ± 0.1; *dnaX36* Δ*polB*, 46 ± 6; *dnaX*[+] Δ*polB dinB*, 0.9 ± 0.2; *dnaX36* Δ*polB dinB*, 29 ± 5; *dnaX*[+] *polBex1*, 8.9 ± 0.3; *dnaX36 polBex1*, 295 ± 30; *dnaX*[+] *polBex1 dinB*, 5.1 ± 0.4; *dnaX36 polBex1 dinB*, 240 ± 13. (C) Mutant frequencies for *lac* $A \cdot T \rightarrow T \cdot A$ transversions in the L (leading-strand) orientation. The mutant frequencies $\pm$ SE values were as follows: *dnaX*[+], 1.1 ± 0.3; *dnaX36*, 3.4 ± 0.6; *dnaX*[+] *dinB*, 1.1 ± 0.2; *dnaX36 dinB*, 4.4 ± 0.5; *dnaX*[+] Δ*polB*, 1.0 ± 0.2; *dnaX36* Δ*polB*, 4.2 ± 0.3; *dnaX*[+] *polBex1*, 2.2 ± 0.3; *dnaX36 polBex1*, 90 ± 7; *dnaX*[+] *polBex1 dinB*, 2.0 ± 0.6; *dnaX36 polBex1 dinB*, 83 ± 5. ND, not done. (D) Mutant frequencies for *lac* $A \cdot T \rightarrow T \cdot A$ transversions in the R (lagging-strand) orientation. The mutant frequencies $\pm$ SE values were as follows: *dnaX*[+], 0.8 ± 0.2; *dnaX36*, 4.1 ± 0.4; *dnaX*[+] *dinB*, 0.8 ± 0.2; *dnaX36 dinB*, 3.1 ± 0.4; *dnaX*[+] Δ*polB*, 0.7 ± 0.2; *dnaX36* Δ*polB*, 5.1 ± 0.4; *dnaX*[+] *polBex1*, 3.3 ± 0.3; *dnaX36 polBex1*, 200 ± 11; *dnaX*[+] *polBex1 dinB*, 3.0 ± 0.4; *dnaX36 polBex1 dinB*, 133 ± 9. ND, not done.

of the mutant frequency, although the frequency does not return to the level for the single *dnaX36* strain. These results indicate that Pol II and Pol IV can compete and that, at least in the absence of Pol II, the *dnaX36* mutator effect has both Pol IV-dependent and Pol IV-independent components.

The role of Pol II was further probed by using the *polBex1* allele. Consistent with findings of previous studies (1), the *polBex1* allele is mutagenic in a wild-type *dnaX*[+] back-

ground. This has been interpreted to indicate that apparently Pol II, even under normal conditions, may have access to the replication fork, serving in an antimutagenic role, likely acting as a backup proofreader for Pol III (1). This editing role becomes increasingly important in the *dnaX36* strain. As seen in Fig. 1, the *dnaX36 polBex1* combination yields a very potent mutator activity, enhancing the effect some 20- to 22-fold for the $G \cdot C \rightarrow T \cdot A$ allele and 26- to

49-fold for the A · T → T · A allele (compare *dnaX36* to *dnaX36 polBex1*). This strong mutator effect resulting from the Pol II proofreading deficiency is not dependent on the action of Pol IV, since the *dnaX36 polBex1 ΔdinB* triple mutant behaves essentially as does the *dnaX36 polBex1* double. Thus, an important fidelity role of Pol II at the chromosomal replication fork of *dnaX36* is revealed.

The τ fidelity mechanism. We have suggested that the *dnaX36* mutator effect is most productively interpreted in terms of a defect in the processing of terminal mismatches (misinsertion errors) produced by the Pol III α-subunit (1, 12, 18, 22, 23). The current data on chromosomal DNA synthesis support this proposal. While most terminal mismatches created by the α subunit are expected to be removed by the ε proofreading subunit, a subset of errors may be refractory to this mechanism and require the action of the τ subunit for resolution. This mechanism operates on both leading and lagging strands. How τ promotes error removal is not yet known, but it may involve facilitating the required conformational change in α to place the mismatch in the exonuclease site. Alternatively, τ may channel the mismatch toward the exonuclease of Pol II or the exonuclease of a third Pol III core that has been proposed to be present at the replication fork (25). Obviously, in the absence of this τ function (as in the *dnaX36* mutant), this mechanism may be inoperative. Pol III may be forced to eventually extend the terminal mismatch, accounting for the *dnaX* mutator effect. On the other hand, our data indicate that the major fate of the mismatch is editing by the exonuclease of Pol II. In fact, more than 90% of the potential mutations (those seen in the *dnaX36 polBex1* mutant) appear to be edited away by Pol II. Thus, Pol II is the primary backup polymerase at the replication fork.

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