Fidelity and Damage Bypass Ability of Schizosaccharomyces pombe Eso1 Protein, Comprised of DNA Polymerase η and Sister Chromatid Cohesion Protein Ctf7*

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DNA polymerase η (Polη) functions in error-free bypass of ultraviolet light-induced DNA lesions, and mutational inactivation of Polη in humans causes the cancer prone syndrome, the variant form of xeroderma pigmentosum (XPV). Both Saccharomyces cerevisiae and human Polη efficiently insert two adenines opposite the two thymines of a cyclobutane pyrimidine dimer. Interestingly, in the fission yeast Schizosaccharomyces pombe, the eso1+ encoded protein is comprised of two domains, wherein the NH2 terminus is highly homologous to Polη, and the COOH terminus is highly homologous to the S. cerevisiae Ctf7 protein which is essential for the establishment of sister chromatid cohesion during S phase. Here we characterize the DNA polymerase activity of S. pombe GST-Eso1 fusion protein and a truncated version containing only the Polη domain. Both proteins exhibit a similar DNA polymerase activity with a low processivity, and steady-state kinetic analyses show that on undamaged DNA, both proteins misincorporate nucleotides with frequencies of 10^-4 to 10^-3. We also examine the two proteins for their ability to replicate a cyclobutane pyrimidine dimer-containing DNA template and find that both proteins replicate through the lesion equally well. Thus, fusion with Ctf7 has no significant effect on the DNA replication or damage bypass properties of Polη. The possible role of Ctf7 fusion with Polη in the replication of Cohesin-bound DNA sequences is discussed.

In Saccharomyces cerevisiae as well as humans, DNA polymerase η functions in error-free replication of UV-damaged DNA. In S. cerevisiae, inactivation of Polη confers enhanced UV sensitivity and leads to an increase in UV-induced mutation frequencies (1–3). In humans, inactivation of Polη results in the cancer prone syndrome, the variant form of xeroderma pigmentosum (4, 5). Cells from variant form of xeroderma pigmentosum patients display a deficiency in the replication of UV-damaged DNA (6–8), and they are hypermutable with UV light (9, 10). Polη is unique among euukaryotic DNA polymerases in its proficient ability to replicate through DNA lesions which distort the DNA helix (5, 11–14). Both yeast and human Polη replicate through a cis-syn thymine-thymine (T-T) dimer with the same efficiency and accuracy as they replicate through the two undamaged Ts (12, 15). The ability of Polη to insert nucleotides opposite distorting DNA lesions and to carry out extension of the nascent DNA strand has suggested that Polη is more tolerant of geometric distortions in DNA than are other DNA polymerases which cannot bypass DNA lesions. Accordingly, both S. cerevisiae and human Polη are low fidelity enzymes, misincorporating nucleotides with a frequency of 10^-2 to 10^-3 (12, 16, 17).

Although Polη is a low fidelity enzyme, it does not contribute to spontaneous mutagenesis, since the rate of spontaneous mutations at several loci examined remains the same in the presence or absence of Polη in S. cerevisiae (18). Thus, Polη may have little or no effect on normal replication, and its function may be primarily restricted to promoting replication through DNA lesions. The Rad6-Rad18 complex, comprised of the ubiquitin conjugating and DNA binding activities (19, 20), may be a key factor in limiting Polη action to damage bypass. Although the mechanism of the Rad6-Rad18 enzyme complex remains unknown, it is possible that ubiquitin conjugation by the Rad6-Rad18 complex leads to dissociation of some protein(s) from the replication machinery stalled at a lesion site, and that, in turn, promotes the assembly of a trans-lesion DNA synthesis polymerase such as Polη into the stalled replication complex. Alternatively, Polη could be kept in an inactive state by its binding to other protein(s), and upon the infliction of damage to DNA, the Rad6-Rad18 mediated protein ubiquitination may stimulate the dissolution of the inhibitory protein(s), thereby activating Polη.

Interestingly, in the fission yeast Schizosaccharomyces pombe, the eso1+--encoded protein is comprised of two domains, of which the NH2-terminal two-thirds is highly homologous to S. cerevisiae and human Polη, and the COOH-terminal third is highly homologous to the S. cerevisiae Ctf7 protein (also called Eco1) (21), an essential protein required for the establishment of sister chromatid cohesion during S phase (21–23). Deletion analyses have indicated that the COOH-terminal Ctf7 portion of Eso1 is sufficient and necessary for sister chromatid cohesion, whereas deletion of the NH2-terminal Polη portion increases the sensitivity to UV irradiation but has no effect on sister chromatid cohesion (21). Thus, although the two proteins are encoded by the same gene, they retain their respective functions in sister chromatid cohesion and damage bypass. The fusion of Polη with Ctf7 in S. pombe raised the possibility that although the two proteins are encoded by separate genes in other species, even there these proteins may associate in vivo, and that association may modulate the function of one or both the proteins. For instance, it could be that association with Ctf7

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1 R. E. Johnson, L. Prakash, and S. Prakash, unpublished observations.
inactivates Pol\(\eta\) and its activation requires that the two proteins dissociate following the Rad6-Rad18-dependent ubiquitination of one or both proteins; alternatively, association with Ctf7 could improve the fidelity and processivity of Pol\(\eta\). Here, we purify the \(S.\) pombe \(eso1\) gene was amplified from the \(S.\) pombe strain JF41 th\(\)a4-D18 ade6-M216 leu1-32 total genomic DNA by polymerase chain reaction using oligonucleotide N7119 (5'-CAGGCGT-TACGATCATGGAATTAGGCAAAAGCAAATTCTC-3') and the oligonucleotide N7118 (5'-GGTCGTCGACGGATCCTCAACTTTCATA-ACACGATCATGGAATTAGGCAAAAGCAAATTCTC-3'), respectively, and the nucleotide oligonucleotide N7117 (5'-GGTCGTCGACGGATCCTCAACTTTCATA-ACACGATCATGGAATTAGGCAAAAGCAAATTCTC-3'), respectively. The amplified DNAs were then digested with Asp-718 and \(H11032\) buffer containing 1 M NaCl, followed by 5 volumes ice-cold low salt buffer (50 mM Tris-HCl, pH 7.5), 1 mM EDTA, 300 mM NaCl, 0.01% Nonidet P-40, 10% glycerol, 25 mM glutathione. Aliquots of 60 \(\mu\)l of extract (Roche Molecular Biochemicals), and lysed at 4 \(\circ\)C. The beads were washed with 10 volumes ice-cold cell breakage buffer (50 mM Tris-HCl, pH 7.5, 1 mM EDTA, 50 mM NaCl, 10% glyc-
The Eso1 and Pol\(\eta\) Proteins of S. pombe

**Fig. 1.** Schematic alignment of *S. pombe* Eso1 protein (SpEso1), *S. cerevisiae* Ctf7 protein (ScCtf7), and *S. cerevisiae* Pol\(\eta\) protein (ScPol\(\eta\)). Regions of homology are indicated by large shaded boxes and nonhomologous sequences are shown as narrow white boxes. Motifs I-V are highly conserved in the Pol\(\eta\)/UmuC/DinB protein family. The *arrow* in Eso1 indicates the position of the truncation for producing the Eso1(1–609) protein containing the entire Pol\(\eta\) domain.

where \(I\) is the intensity of gel band \(x\). In a single DNA binding event, it takes \(N-1\) consecutive steps, each occurring with a probability \(P\), starting at gel band 1 to reach any gel band \(N\). Thus, the relationship between the fraction of polymerase molecules that incorporated at least \(N\) nucleotides, \(\phi_N\), and the processivity, \(P\), is expressed in the following equation (Equation 4),

\[
\phi_N = P^{N-1} \quad \text{(Eq. 4)}
\]

Consequently, we graphed \(\phi_N\), the fraction of polymerase molecules that incorporated at least \(N\) nucleotides, versus \(N-1\), and obtained a value for the processivity, \(P\), from the best fit curve to Equation 4 using nonlinear regression (SigmaPlot 4.0). The average number of nucleotides incorporated per DNA binding event (\(1/(1 - P)\)) was then calculated.

**RESULTS**

The Eso1 Protein of *S. pombe*—The amino-terminal two-thirds of the *S. pombe* eso1\(\perp\)-encoded protein shares 23% identical and 34% similar amino acid residues with the *S. cerevisiae* Pol\(\eta\), and the COOH-terminal one-third of the protein shares 24% identical and 44% similar residues with the *S. cerevisiae* Ctf7 protein (21), which is highly conserved among eukaryotes and plays an essential role in the establishment of sister chromatid cohesion during DNA replication (21–23). Fig. 1 depicts the conserved motifs shared between Eso1 and the *S. cerevisiae* Pol\(\eta\) and Ctf7 proteins. Two C\(_2\)H\(_2\) zinc finger motifs are present in Eso1, one of which corresponds to the motif present toward the COOH terminus of Pol\(\eta\) and the other corresponds to the motif present toward the NH\(_2\) terminus of Ctf7. The five highly conserved motifs found in the Rad30/UmuC/DinB protein family (28), are present in the Pol\(\eta\) portion of Eso1.

To test for the influence of the COOH-terminal Ctf7-like portion on the polymerase activity of Eso1 protein, we expressed in *S. cerevisiae* both the full-length Eso1 protein (872 amino acids) and a truncated Eso1 protein that contains only the NH\(_2\)-terminal 609 amino acids, and which corresponds to the Pol\(\eta\) domain, as fusions with the glutathione S-transferase protein. The GST-Eso1 and GST-Pol\(\eta\) proteins were affinity purified to near homogeneity (Fig. 2A) and their DNA synthesis and damage bypass properties were analyzed.

**DNA Polymerase Activity of *S. pombe* Eso1 and Pol\(\eta\) Proteins**—To test for DNA polymerase activity of *S. pombe* Eso1 and Pol\(\eta\) proteins, various concentrations of purified proteins were incubated with labeled primer-template DNA substrate in the presence of all four deoxynucleotides, and reaction products were resolved on a denaturing polyacrylamide gel. As shown in Fig. 2B, both proteins exhibit nearly equivalent DNA polymerizing ability.

**Fidelity of *S. pombe* Eso1 and Pol\(\eta\) Proteins**—Fidelity measures the likelihood that a polymerase will incorporate the correct versus the incorrect deoxynucleotide opposite a template residue. We used steady-state kinetics to measure the fidelity of *S. pombe* Eso1 and Pol\(\eta\) proteins opposite all four undamaged template nucleotides, as described under “Materials and Methods.” The incorporation of either the correct or incorrect deoxynucleotide was quantitated and used to calculate the \(V_{max}\) and \(K_m\) values.

*S. pombe* Eso1 protein (5 nM) was incubated with the primer-template DNA and various concentrations of one of the four deoxynucleotides in a standing-start reaction. As shown in Fig. 3A, to examine the incorporation opposite template G, the concentration of incorrect and correct deoxynucleotide was varied from 0 to 1000 \(\mu\)M, and from 0 to 20 \(\mu\)M, respectively. The kinetics of single deoxynucleotide incorporation by *S. pombe* Eso1 protein opposite the template G are shown in Fig. 3B. These data were fit to the Michaelis-Menten equation (Equation 1), and used to calculate the apparent \(K_m\) and \(V_{max}\) parameters. As shown in Table I, the \(f_{inc}\) values for the Eso1 protein range from 2.4 \(\times\) 10\(^{-4}\) to 6.5 \(\times\) 10\(^{-3}\). The \(f_{inc}\) values were similarly calculated for the Pol\(\eta\) protein. As shown in Table II, Pol\(\eta\), misincorporates nucleotides with nearly the same efficiencies as the Eso1 protein. Fig. 4 compares the efficiencies of \(V_{max}/K_m\) of correct and incorrect deoxynucleotide incorporation opposite templates G, A, T, and C by *S. pombe* Eso1 and Pol\(\eta\) proteins. This comparison shows that the two proteins incorporate nucleotides with nearly the same efficiencies. Thus, the presence of the Ctf7 protein in the COOH terminus of Eso1 has little, if any, effect on Pol\(\eta\)’s ability to incorporate the correct or wrong nucleotides opposite undamaged template bases.

**Processivity of *S. pombe* Pol\(\eta\) and Eso1 Proteins**—Processivity is a measure of the number of deoxynucleotides a polymerase incorporates in a single DNA binding event. Processivity is expressed quantitatively as the probability, \(P\), that following each nucleotide incorporation, the polymerase will move ahead to incorporate at least one additional deoxynucleotide (27). To ensure that we were measuring the activity of a single DNA binding event, we included excess, nonradiolabeled sonicated herring sperm DNA to trap any polymerase molecules that dissociated from the DNA. The Eso1 (Fig. 5A, lanes 1–3) or Pol\(\eta\) (Fig. 5A, lanes 7–9) proteins were preincubated with radiolabeled primer-template DNA substrate for 1 h before the addition of excess herring sperm DNA and all four deoxynucleotides. To determine that the excess herring sperm DNA was indeed sufficient to prevent the re-binding of Eso1 or Pol\(\eta\) proteins to the radiolabeled DNA substrate, the Eso1 (Fig. 5A, lanes 4–6) or Pol\(\eta\) (Fig. 5A, lanes 10–12) proteins were prein-
FIG. 3. Kinetics of nucleotide incorporation by *S. pombe* Eso1 protein. A, deoxynucleotide incorporation opposite a template G residue. Eso1 protein (5 nM) was incubated for 2–20 min at 25 °C with the primer-template DNA substrate (50 nM) and increasing concentrations of nucleotide. The samples were quenched and analyzed by denaturing PAGE. The extended primer (n = 0) and the extended primers (N = 1 and 2) are indicated. B, quantitation of deoxynucleotide incorporation reactions. For each deoxynucleotide opposite the template, the observed rate of deoxynucleotide incorporation is graphed as a function of deoxynucleotide concentration. The data were fit using Equation 1, and the resulting *V* _\(_{\text{max}}\)_ and *K* _\(_{\text{m}}\)_ parameters are listed in Table I.

**TABLE I**

| Primer-Template | *V* _\(_{\text{max}}\)_ (nM/min) | *K* _\(_{\text{m}}\)_ (nM) | *V* _\(_{\text{max}}\)/*K* _\(_{\text{m}}\)_ | *f* _\(_{\text{inc}}\)_ |
|-----------------|---------------------------------|-----------------|-----------------|-----------------|
| G · G           | 0.31 ± 0.01                     | 140 ± 20        | 2.2 × 10⁻²      | 1.2 × 10⁻³      |
| A · G           | 0.075 ± 0.004                   | 65 ± 12         | 1.2 × 10⁻³      | 6.7 × 10⁻⁴      |
| T · G           | 0.51 ± 0.02                     | 110 ± 20        | 4.6 × 10⁻³      | 2.6 × 10⁻³      |
| C · G           | 4.8 ± 0.2                       | 27 ± 0.4        | 1.8             | 1               |
| G · A           | 0.20 ± 0.02                     | 250 ± 100       | 8.0 × 10⁻⁴      | 1.3 × 10⁻³      |
| A · A           | 0.53 ± 0.03                     | 130 ± 20        | 4.1 × 10⁻³      | 6.5 × 10⁻³      |
| T · A           | 5.6 ± 0.6                       | 8.9 ± 2.1       | 0.63            | 1               |
| C · A           | 0.39 ± 0.02                     | 480 ± 70        | 8.1 × 10⁻⁴      | 1.3 × 10⁻³      |
| G · T           | 1.3 ± 0.2                       | 2000 ± 500      | 6.5 × 10⁻⁷      | 7.6 × 10⁻⁴      |
| A · T           | 2.9 ± 0.2                       | 3.4 ± 0.7       | 0.85            | 1               |
| T · T           | 0.36 ± 0.05                     | 180 ± 40        | 2.0 × 10⁻³      | 2.4 × 10⁻³      |
| C · T           | 0.41 ± 0.08                     | 290 ± 160       | 1.4 × 10⁻³      | 1.6 × 10⁻³      |
| G · C           | 10 ± 1                          | 5.9 ± 1.9       | 1.7             | 1               |
| A · C           | 1.4 ± 0.2                       | 1400 ± 400      | 1.0 × 10⁻³      | 5.9 × 10⁻⁴      |
| T · C           | 0.72 ± 0.07                     | 1800 ± 300      | 4.0 × 10⁻⁴      | 2.4 × 10⁻⁴      |
| C · C           | 0.12 ± 0.01                     | 46 ± 11         | 2.6 × 10⁻³      | 1.5 × 10⁻³      |

cubated with the radiolabeled primer-template DNA substrate and the excess DNA trap for 1 h before the addition of all four deoxynucleotides. The lack of any DNA synthesis in these reactions (Fig. 5A, lanes 4–12) confirmed the adequacy of excess herring sperm DNA to trap all Eso1 or Pol η molecules.

The gel band intensities of the nucleotide incorporation products at the 15-s time point were used to calculate the processivity, *P*, and the average number of nucleotides incorporated per DNA binding event (see “Materials and Methods”). Fig. 5B is a plot of *φ* _\(_{\text{inc}}\)_, the fraction of polymerase molecules that incorporated at least N nucleotides, versus N-1 for the Eso1 protein. From the best fit curve to Equation 4, we obtained a value for *P* equal to 0.53 ± 0.01, which means that for each nucleotide incorporation event, the Eso1 protein has a 53% chance of moving ahead to incorporate at least one additional nucleotide. Thus, the average number of nucleotides incorporated by the Eso1 protein per DNA binding event is 2.1. Likewise, Fig. 5C is the analogous plot for Pol η. From the best fit curve to Equation 4, we obtained a value for *P* equal to 0.61 ± 0.01. Thus, the average number of nucleotides incorporated by Pol η per DNA binding event is 2.6.

**T-T Dimer Bypass by *S. pombe* Eso1 and Pol η Proteins—**The ability of Eso1 and Pol η proteins to replicate through a cis-syn T-T dimer was assessed using a standing start assay. As shown in Fig. 6A, both proteins are able to incorporate a deoxynucleotide opposite the 3' T of the dimer and to extend from it, and the DNA synthesis activity on the damaged DNA is as robust.
subunits is loaded onto chromosomes at the end of G1. Another cohesion complex consisting of the Scc1, Scc3, Smc1, and Smc3 proteins of S. pombe.

Eso1 and Pol\(\eta\) are opposed to the two Ts of the dimer. In all these properties, the equally well and both predominantly insert two A residues per DNA nucleotide with frequencies ranging from 2 \(\times\) 10\(^{-2}\) to 2 \(\times\) 10\(^{-4}\). Also, the two proteins replicate a cis-syn T-T dimer equally well and both predominantly insert two A residues opposite each of the Ts of the T-T dimer.

**DISCUSSION**

The fusion of Pol\(\eta\) to the sister chromatid cohesion protein Ctf7 in the S. pombe Eso1 protein has presented the opportunity to determine whether the fusion with Ctf7 affects Pol\(\eta\) function. Our results indicate that the DNA synthesis activity of Pol\(\eta\) is not affected by fusion to Ctf7, as the Eso1 and Pol\(\eta\) proteins synthesize DNA with remarkably similar efficiencies and fidelities, and on undamaged DNA, they misincorporate nucleotides with frequencies ranging from 2 \(\times\) 10\(^{-2}\) to 2 \(\times\) 10\(^{-4}\). Also, the two proteins replicate a cis-syn T-T dimer equally well and both predominantly insert two A residues opposite each of the Ts of the dimer. In all these properties, the S. pombe Eso1 and Pol\(\eta\) proteins resemble S. cerevisiae and human Pol\(\eta\).

Pol\(\eta\) is a low processivity enzyme, dissociating from DNA quite frequently. DNA polymerases achieve processive synthesis by associating with a multimeric ring \(\beta\) clamp in Escherichia coli or PCNA in eukaryotes. T7 polymerase increases its processivity by forming a one-to-one complex with E. coli thioredoxin (29, 30). The processivity of Pol\(\eta\), however, is not affected by its fusion to Ctf7. Both the Eso1 and Pol\(\eta\) proteins exhibit low processivity, inserting 2–3 nucleotides per DNA binding event.

Although Ctf7 does not activate or inactivate the DNA polymerizing activity or T-T dimer bypass ability of Pol\(\eta\), fusion with Ctf7 may enable Pol\(\eta\) to function in sister chromatid cohesion. Genetic studies in S. cerevisiae have suggested that a cohesion complex consisting of the Sec1, Sec3, Smc1, and Smc3 subunits is loaded onto chromosomes at the end of G1. Another protein, Sec2, although not a stoichiometric Cohesin subunit, is required for the association of the cohesion complex with chromosomes (23). The sixth protein, Ctf7, is neither a subunit of the Cohesin complex nor is it required for the association of Cohesin with chromosomes (23). Ctf7, however, is essential for the establishment of cohesion during DNA replication, but it is not required for the maintenance of cohesion during G2 and M phases (22, 23). One possible role for the fusion of Ctf7 with Pol\(\eta\) in the Eso1 protein is that it promotes replication through

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**Fig. 4.** Comparison of efficiency (\(V_{max}/K_m\)) of deoxynucleotide incorporation by S. pombe Eso1 and Pol\(\eta\) proteins. The efficiency (y axis) of incorporation of each of the four nucleotides opposite each template base G, A, T, and C (x axis) is shown for Eso1 (□) and Pol\(\eta\) (■) proteins. In the base pairs shown, the first base represents the incoming nucleotide, and the second base is in the template.

**Fig. 5.** Processivity of S. pombe Eso1 and Pol\(\eta\) proteins. A, DNA synthesis by Eso1 and Pol\(\eta\) proteins resulting from a single DNA binding event. 50 nM Eso1 (lanes 1–3) or Pol\(\eta\) (lanes 7–9) was preincubated with 50 nM primer-template DNA for 1 h at 25 °C, and the reactions were initiated by the addition of 100 \(\mu\)M of each of four dNTPs, 5 mM MgCl\(_2\), and 1 mg/ml sonicated herring sperm DNA trap. Reactions were quenched after 15 or 30 s, and the samples were resolved by denaturing PAGE. The positions of the unextended primer (n = 0) and extended primers (n = 1–11) are indicated. As a control, 1 mg/ml sonicated herring sperm DNA trap was added to the preincubation mixture containing Eso1 (lanes 4–6) or Pol\(\eta\) proteins (lanes 10–12), and the reactions were initiated by the addition of 100 \(\mu\)M of each of four dNTPs and 5 mM MgCl\(_2\). B and C, graphs of \(\phi_n\), the fraction of polymerase molecules that incorporated at least N nucleotides, versus N-1 for the Eso1 and Pol\(\eta\) proteins, respectively. The solid lines reflect the best fit curves to Equation 4 and were used to obtain values for the processivity, P, as described under “Materials and Methods.”
chromosomal sites where Cohesin has been deposited onto DNA, and replication through such sites may be a prerequisite for the formation of protein links between Cohesin-bound sister chromatids.

While the above model explains the requirement of Ctf7 in S. cerevisiae and S. pombe for the establishment of sister chromatin cohesion during S phase, it fails to account for the fact that deletion of Polγ has no apparent effect on sister chromatin cohesion in either yeast species. One possible explanation for this discrepancy is the involvement of yet two other highly related proteins, Trf4 and Trf5, in sister chromatin cohesion. A trf4 ts trf5Δ double mutant is unable to complete S phase, and results in failure of cohesion between the replicated sister chromatids (31). The Trf proteins are members of the β-polymerase superfamily, and accordingly, a DNA polymerase activity has been identified in Trf4 (31). A role for the Trf4 and Trf5 polymerases in the replication of Cohesin-bound DNA has been previously proposed (31). The fact that the Trf4 and Trf5 proteins are essential for the establishment of sister chromatin cohesion suggests that these polymerases are indispensable for the replication of Cohesin-bound DNA sequences, whereas the dispensability of Polγ for sister chromatin cohesion would suggest that this protein plays a much less critical role in the replication of Cohesin-bound DNA. Polγ may have an accessory role in the replication of Cohesin-bound DNA, where it promotes replication through some sites by the Trf4 or Trf5 polymerase. Polγ may act at such sites in a manner analogous to its role in damage bypass where it salvages the replication fork stalled at a lesion site.

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