Structural Basis of Recruitment of DNA Polymerase ζ by Interaction between REV1 and REV7 Proteins*

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The abbreviations used are: Pol, DNA polymerase; TLS, translesion DNA synthesis.

REV1, REV3, and REV7 are pivotal proteins in translesion DNA synthesis, which allows DNA synthesis even in the presence of DNA damage. REV1 and REV3 are error-prone DNA polymerases and function as inserter and extender polymerases in this process, respectively. REV7 interacts with both REV1 and REV3, acting as an adaptor that functionally links the two, although the structural basis of this collaboration remains unclear. Here, we show the crystal structure of the ternary complex, composed of the C-terminal domain of human REV1, REV7, and a REV3 fragment. The REV1 C-terminal domain adopts a four-helix bundle that interacts with REV7. A linker region between helices 2 and 3, which is conserved among mammals, interacts with the β-sheet of REV7. Remarkably, the REV7-binding interface is distinct from the binding site of DNA polymerase η or ζ. Thus, the REV1 C-terminal domain might facilitate polymerase switching by providing a scaffold for both inserter and extender polymerases to bind. Our structure reveals the basis of DNA polymerase ζ (a complex of REV3 and REV7) recruitment to the stalled replication fork and provides insight into the mechanism of polymerase switching.

Background: REV1 and DNA polymerase ζ (Polζ), a complex of catalytic REV3 and non-catalytic REV7 subunits, are involved in translesion DNA synthesis (TLS).

Results: The mechanism of REV1-Polζ interaction is revealed by the crystal structure of the REV1-Polζ complex.

Conclusion: Polζ is recruited by REV1-REV7 interaction.

Significance: Revealing the mechanism of REV1-Polζ interaction provides a new strategy to modulate TLS for cancer therapy.

REV1 and DNA polymerase ζ (Polζ) are involved in translesion DNA synthesis, which allows DNA synthesis even in the presence of DNA damage. REV1 and REV3 are error-prone DNA polymerases and function as inserter and extender polymerases in this process, respectively. REV7 interacts with both REV1 and REV3, acting as an adaptor that functionally links the two, although the structural basis of this collaboration remains unclear. Here, we show the crystal structure of the ternary complex, composed of the C-terminal domain of human REV1, REV7, and a REV3 fragment. The REV1 C-terminal domain adopts a four-helix bundle that interacts with REV7. A linker region between helices 2 and 3, which is conserved among mammals, interacts with the β-sheet of REV7. Remarkably, the REV7-binding interface is distinct from the binding site of DNA polymerase η or ζ. Thus, the REV1 C-terminal domain might facilitate polymerase switching by providing a scaffold for both inserter and extender polymerases to bind. Our structure reveals the basis of DNA polymerase ζ (a complex of REV3 and REV7) recruitment to the stalled replication fork and provides insight into the mechanism of polymerase switching.

Genomic DNA is constantly damaged by various factors, including endogenous and exogenous agents. The majority of DNA lesions stall replicative DNA polymerase (Pol) δ or Polε, resulting in the arrest of DNA replication, which causes lethal effects such as genomic instability and cell death. To avoid replication arrest, cells employ a strategy termed DNA damage tolerance, including translesion DNA synthesis (TLS). TLS is a mechanism that releases replication blockade and allows continuing DNA synthesis even in the presence of DNA damage. During TLS, DNA is synthesized using damaged DNA template by specialized error-prone DNA polymerases (TLS polymerases), including REV1, Polη, Polκ, Polε, and Polζ. It is generally thought that TLS includes two steps performed by at least two types of TLS polymerase, namely inserter and extender polymerases (1, 2). In the first step, an inserter polymerase classified as a Y-family DNA polymerase, such as REV1, Polη, Polκ, and Polε (3), incorporates a nucleotide opposite the DNA lesion instead of the stalled replicative polymerase at the damage site. In the second step, the extender polymerase Polζ extends additional nucleotides. Polζ is composed of two subunits, REV3 and REV7. REV3 is a catalytic subunit of Polζ and is classified as a B-family DNA polymerase. REV7 is a non-catalytic subunit of Polζ and interacts with the central region of REV3 (Fig. 1) (4). Yeast Rev7 stimulates the polymerase activity of yeast Rev3 (5), whereas the biochemical properties of mammalian Polζ are still unclear. Recently, we reported the crystal structure of human REV7 in complex with a human REV3 fragment, revealing the mechanism of the interaction between REV7 and REV3, and showed that the interaction is indispensable for the cellular function of REV3 (6). REV1 is a Y-family DNA polymerase specialized for abasic lesion (apurinic/apyrimidinic site) and incorporates a cytokine. Independent from its polymerase function, REV1 interacts with other Y-family DNA polymerases (Polη, Polκ, and Polε) through its C-terminal domain (7), thereby providing a scaffold for assembly of TLS polymerases at a damage site. Furthermore, it has been reported that Rev1-Polζ interaction stimulates the activity of Polζ in yeast (8). Interestingly, REV7, a non-catalytic subunit of Polζ, interacts with the C-terminal domain of REV1 (Fig. 1) (7, 9). This implies that REV1-REV7 interaction should exclude inserter polymerases from REV1 for polymerase switching to the extender polymerase. Thus, REV1, REV3, and REV7 functionally collaborate in TLS.

In fact, chicken DT40 cells deficient in one of the three REV proteins and those deficient in all three proteins show hypersensitivity to various genotoxic treatments (10). Furthermore,
we have recently shown that the C-terminal domain of human REV1, REV7, and a REV3 fragment form a ternary complex and have proposed that REV7 acts as an adaptor protein that functionally links REV1 and REV3 (6). Recently, it has been shown that REV1, REV3, and REV7 are also involved in homologous recombination, a key pathway for the repair of complex lesions, including double-strand breaks (11). Furthermore, it has been reported that suppression of REV3 sensitizes drug-resistant lung tumors to chemotherapy and that suppression of REV1 inhibits both cisplatin- and cyclophosphamide-induced mutagenesis, suggesting that inhibition of REV1 and/or Polζ might be a new strategy for cancer chemotherapy (12, 13). However, the structural basis of REV1-Polζ interaction remains unknown. Here, we show the crystal structure of a ternary complex composed of the C-terminal domain of human REV1, REV7, and a REV3 fragment, revealing the structural basis of the recruitment mechanism of Polζ, in which the REV1 C-terminal domain provides a scaffold for both inserter and extender polymerases and thereby might facilitate switching from an inserter polymerase to the extender polymerase Polζ.

**EXPERIMENTAL PROCEDURES**

Protein Preparation and Crystallization—The preparation of human REV1 (residues 1140–1251) and the crystallization of the ternary complex have been described previously (14). In brief, human REV1 (residues 1140–1251) with an N-terminal His tag was expressed in *Escherichia coli* BL21(DE3) cells. The protein was purified by column chromatography using nickel-Sepharose 6 Fast Flow, HiTrap Q HP, and HiLoad 16/60 Superdex 75 prep grade columns (GE Healthcare). The human REV7(R124A) mutant in complex with a REV3 fragment was prepared as reported previously (15). Prior to crystallization, the ternary complex was prepared by mixing REV1 and REV7-REV3 complex in an equimolar ratio. Trigonal crystals of the ternary complex were obtained by the hanging drop vapor diffusion method using a reservoir solution containing 162 mM carboxyethyl)phosphine HCl at 20 °C.

Structure Determination—X-ray diffraction data were collected at 1.6 mg/ml, frozen in liquid nitrogen, and stored at −80 °C.

**TABLE 1**

| Data collection and refinement statistics |
|-----------------------------------------|
| Wavelength (Å)                          | 1.0000 |
| Space group                             | P3,21  |
| a = b (Å)                               | 75.0   |
| c (Å)                                   | 123.3  |
| γ                                        | 120°   |
| Resolution (Å)                          | 19.65-2.80 |
| Observed reflections                    | 72,199 |
| Unique reflections                      | 10,306 |
| Rmerge                                  | 0.051 (0.584) |
| Completeness (%)                        | 99.6 (100) |
| (I/σI)                                  | 20.6 (2.9) |

Refinement

| Resolution (Å) | 20.0-2.80 |
| Free reflections | 9795 |
| R               | 0.191 |
| Rmerge          | 0.239 |
| Root mean square deviation                 | 0.014 |
| Bond lengths (Å)                                    | 1.797* |
| Bond angles                                          | 1.797* |
| Protein Data Bank code                             | 3VU7 |

Overall Structure of the Ternary Complex—The crystal structure of the human REV1 C-terminal domain in complex with REV7 bound to a REV3 fragment has been determined at 2.8 Å resolution. The ternary complex was determined by molecular replacement with the program MolREP (18) using a structure of REV7(R124A) bound to a REV3 fragment as a search model (6). The resulting difference Fourier map clearly indicated the four-helix bundle structure of REV1 bound to REV7. The structure was built with the program Coot (19) and refined with the program REFMAC (20). Data collection and refinement statistics are given in Table 1.

**Pulldown Assays**—cDNA for human REV1 (residues 1140–1251) was cloned in the pGEX-6P-1 vector (GE Healthcare) at the BamHI-XhoI sites. The expression vector encodes GST-fused REV1 (residues 1140–1251). Mutations in GST-REV1 were introduced using the QuikChange protocol (Stratagene). GST-REV1 was overexpressed in *E. coli* JM109 by isopropyl β-D-thiogalactopyranoside induction. Harvested cells were disrupted by sonication in 50 mM Tris-HCl (pH 7.4) and 500 mM NaCl and clarified by centrifugation. The supernatant was applied to glutathione-Sepharose 4B resin (GE Healthcare) equilibrated with 50 mM Tris-HCl (pH 7.4) and 500 mM NaCl. GST-REV1 was eluted with 50 mM Tris-HCl (pH 7.4) and 500 mM NaCl. GST-REV1 was eluted with 50 mM Tris-HCl (pH 7.4) and 500 mM NaCl. The resin was washed with 50 mM Tris-HCl (pH 7.4) and 2.0 mM NaCl and then re-equilibrated with 50 mM Tris-HCl (pH 7.4) and 500 mM NaCl. GST-REV1 was eluted with 50 mM Tris-HCl (pH 8.5), 500 mM NaCl, and 50 mM reduced glutathione. Purified GST-REV1 was concentrated up to 1.6 mg/ml, frozen in liquid nitrogen, and stored at −80 °C.

Purified His-REV7(R124A)-REV3 (15) was incubated with nickel-Sepharose 6 Fast Flow resin equilibrated with 50 mM HEPES-NaOH (pH 7.4), 500 mM NaCl, and 20 mM imidazole. Purified GST-REV1 was then incubated with the resin. The resin was washed five times with 50 mM HEPES-NaOH (pH 7.4), 1.5 mM NaCl, and 20 mM imidazole. Bound proteins were analyzed by SDS-PAGE with Coomassie Brilliant Blue staining. We performed pulldown assays at least three times and obtained consistent results. Band intensities were calculated with the NIH ImageJ program.

**RESULTS AND DISCUSSION**

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The REV1 C-terminal domain is composed of four α-helices (αA<sup>R1</sup>, αB<sup>R1</sup>, αC<sup>R1</sup>, and αD<sup>R1</sup>) and forms right-handed helical folding, resulting in a four-helix bundle structure (Fig. 2B). The bundle structure is maintained by hydrophobic interactions (Fig. 2C). The region between αB<sup>R1</sup> and αC<sup>R1</sup> and the C-terminal region of REV1 interact with the C-terminal β-sheet of REV7 (β<sup>R7</sup> and β8<sup>R7</sup>) and additionally with β4<sup>R7</sup> (Fig. 2A). The REV3 fragment bound to REV7 does not contact the REV1 C-terminal domain.

**Interaction between REV1 and REV7**—We have already shown that Leu-186 of REV7 is a crucial residue for REV1 binding and that Gln-200 and Tyr-202 are significantly involved in REV1 binding by comprehensive mutations in REV7 coupled with pulldown assays (6). The structure clearly reveals detailed interaction between REV7 and REV1 (Figs. 2A and 3A). Most consistent with our previous result, Leu-186 and Tyr-202 of REV7 form hydrophobic interactions with Leu-1203, Tyr-1244, and Leu-1248 of REV1, which form a “hydrophobic cage” to accommodate Leu-186 of REV7. The side chain of Gln-200 of REV7 forms multiple hydrogen bonds with the main chains of Lys-1201 and Leu-1203 and the side chain of Tyr-1244 of REV1. Pro-184, Ile-187, Pro-188, and Thr-191 in β4<sup>R7</sup> and Glu-204 and Glu-205 in β7<sup>R7</sup> are also involved in the REV1-REV7 interaction (Fig. 3A). Additionally, Glu-101 in β4<sup>R7</sup> interacts with...
the side chain of Lys-1201 of REV1. To clarify the significant interaction between REV1 and REV7, we performed pulldown assays using mutant REV1 proteins (Fig. 3B). As expected because of the structure, the L1203A, Y1244A, or L1248A mutation greatly impaired REV7 binding (Fig. 3B, lanes 4, 7, and 8). The D1202A, E1204A, or K1249A mutation also reduced REV7 binding (Fig. 3B, lanes 3, 5, and 9). These results suggest that hydrophobic interactions are more significant than electrostatic interactions in the REV1-REV7 interaction. Asp-1202 has no apparent interaction with REV7, whereas Asp-1202 contacts Lys-1205 of REV1 (Fig. 3A), suggesting that the interaction could be involved in the structural stabilization of REV1. Taken together with our present and previous works (6), the hydrophobic interactions provided by Leu-186 of REV7 and the hydrophobic cage composed of Leu-1203, Tyr-1244, and Leu-1248 of REV1 are most crucial in the REV1-REV7 interaction. Furthermore, mutation of residues involved in the bundle structure of the REV1 C-terminal domain (W1175A or W1225A) significantly impaired REV7 binding (Figs. 2B and 3B, lanes 2 and 6), indicating that the bundle structure is indispensable for REV7 binding. Consistent with these results, size exclusion chromatography showed that a truncated REV1 C-terminal domain (residues 1130–1223), lacking both AspR and the C-terminal region, did not interact with REV7 (data not shown).

**Structural Comparison with Mad2 Complexes**—The structure of the REV7-REV3 complex bound to REV1 is basically identical to the REV1-free structure (6). The C-terminal region (termed the “safety belt”) of REV7 wraps around the REV3 fragment, resulting in a knot structure. REV7, a HORMA family
protein (21), was identified as a homolog of Mad2, which is involved in the spindle assembly checkpoint during mitosis, and thus, REV7 is alternatively termed Mad2L2, Mad2B, and Mad2B. Mad2 undergoes a striking conformational change from the open (termed O-Mad2) to the closed (termed C-Mad2) form, in which the β-sheet structure of the C-terminal region (termed the safety belt) is rearranged by interaction with partner proteins (22). Based on the analogy with Mad2, REV7 could also employ a conformational change of the safety belt upon REV3 binding, resulting in the closed form of REV7. The present structure obviously indicates that the closed safety belt is required for interaction with REV1. Our results do not exclude the possibility of direct REV1–REV3 association. However, the REV7–REV3 interaction is indispensable for REV3 function (6), indicating that the REV1–REV7 interaction could be a major determinant for the recruitment of Polζ.

Mad2 has two independent binding sites for different proteins; one is the safety belt region flanked by the αB helix, where Mad1 or Cdc20 interacts with Mad2, and the other is the αC helix, which is the binding site of O-Mad2 (23) or Mad3 (BubR1 in metazoans) in the mitotic checkpoint complex (24) for checkpoint activation or p31comet (Mad2L1-binding protein) (25) for checkpoint inactivation. In contrast to O-Mad2, Mad3, or p31comet in those Mad2 complexes, REV1 interacts with the β-sheet of the safety belt of REV7 and does not contact αC (Fig. 4). Thus, the C-terminal β-sheet is the new binding site of HORMA proteins, probably unique to REV7.

Implication for Polymerase Switching—While this manuscript was in preparation, NMR structures of the human REV1 C-terminal domain in complex with REV1-interacting region (RIR) peptides of human Polζ (amino acids 524–539) and the mouse Rev1 C-terminal domain in complex with a RIR peptide of mouse Polk (amino acids 560–582) were reported (26, 27). The structures reveal that the RIR forms a helical structure and binds to a hydrophobic surface composed of αB and αC of mouse Rev1 (Fig. 5). Yeast two-hybrid assay predicted that a region between αB and αC of mouse Rev1 is important for interaction with mouse Rev7 (27). Our structure reveals that the β-sheet of REV7 interacts with the region between αB and αC, and the C-terminal region of REV1 follows αD. Remarkably, the RIR-binding site is far different from the REV7-binding site of REV1, implying that Polζ or Polk binding does not disturb REV7 binding to the REV1 C-terminal domain, resulting in a quaternary complex (Fig. 5). Therefore, switching from an inserter polymerase to Polζ might be regulated by a complex mechanism on the REV1 C-terminal domain. In fact, the little finger domain of yeast Rev1 has been shown to interact with a C-terminal region of Rad30 (a yeast homolog of Polζ) (28). To clarify the switching mechanism, including complicated protein–protein interactions by TLS polymerases, further structural analyses of more high order complexes will be required. These are our future subjects.

Here, we have shown how the REV1 C-terminal domain interacts with REV7, revealing the structural basis of recruitment of Polζ. The interaction of REV7 with REV1 is distinct from that of Mad2 with O-Mad2, Mad3, or p31comet (29). Thus, the REV1-binding site of REV7 is a new target to modulate the DNA damage response, including TLS and homologous recombination, and our structure provides a novel strategy to design a specific inhibitor of the REV1-Polζ complex for cancer therapy.

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FIGURE 4. Structural comparison with the mitotic checkpoint complex. The structure of the mitotic checkpoint complex (Protein Data Bank code 4AEZ) is superimposed on that of the REV1-REV7-REV3 complex. The colors of REV1, REV7, and REV3 are as described in the legend to Fig. 28. Mad2, Cdc20, and Mad3 in the mitotic checkpoint complex are shown in pale blue, pale yellow, and gray, respectively. For clarification, the WD40 domain of Cdc20 and the tetratricopeptide repeat domain of Mad3 have been omitted.

FIGURE 5. Structural implication for the quaternary complex with Polζ or Polk. The NMR structure of the REV1 C-terminal domain in complex with the Polζ (Protein Data Bank code 2LSK) or Polk (Protein Data Bank code 2LSJ) peptide is superimposed on the crystal structure of the REV1-REV7-REV3 complex. REV1 in the Polζ and Polk complexes is shown in pink and light pink, respectively. The Polζ and Polk peptides are shown in cyan and pale cyan, respectively. The colors of REV1, REV7, and REV3 are as described in the legend to Fig. 28.
Structure of the REV1-REV7-REV3 Ternary Complex

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