Human Xeroderma Pigmentosum Group A Protein Interacts with Human Replication Protein A and Inhibits DNA Replication*

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Human replication protein A (RPA; also known as human single-stranded DNA binding protein, or HSSB) is a multisubunit complex involved in both DNA replication and repair. While the role of RPA in replication has been well studied, its function in repair is less clear, although it is known to be involved in the early stages of the repair process. We found that RPA interacts with xeroderma pigmentosum group A complementing protein (XPAC), a protein that specifically recognizes UV-damaged DNA. We examined the effect of this XPAC-RPA interaction on in vitro simian virus 40 (SV40) DNA replication catalyzed by the monoproteinase system. XPAC inhibited SV40 DNA replication in vitro, and this inhibition was reversed by the addition of RPA but not by the addition of DNA polymerase α-primase complex, SV40 large tumor antigen, or topoisomerase I. This inhibition did not result from an interaction between XPAC and single-stranded DNA (ssDNA), or from competition between RPA and XPAC for DNA binding, because XPAC does not show any ssDNA binding activity and, in fact, stimulates RPA’s ssDNA binding activity. Furthermore, XPAC inhibited DNA polymerase α activity in the presence of RPA but not in RPA’s absence. These results suggest that the inhibitory effect of XPAC on DNA replication probably occurs through its interaction with RPA.

Replication protein A (RPA; also known as human single-stranded DNA binding protein, or HSSB), is an eukaryotic single-stranded DNA binding protein that contains three tightly associated subunits of 70, 34, and 11 kDa (p70, p34, and p11, respectively) (1–3). It is required for DNA replication, nucleotide excision repair, and homologous recombination (1–6), suggesting that it has multiple functions in DNA metabolic processes. The p34 subunit of RPA is phosphorylated at the G2/S boundary and dephosphorylated during mitosis (7, 8). This phosphorylation event can also be induced by DNA damage (9, 10). Since DNA damage induces the inhibition of replication, RPA and the phosphorylation of its p34 subunit may play a role in the regulation of DNA replication (10).

During the initiation of simian virus 40 (SV40) DNA replication, RPA interacts with SV40 large tumor antigen (T-ag) and the DNA polymerase α-primase complex (pol α-primase) (11, 12), which appears to be essential for DNA unwinding (12). Human RPA cannot be replaced at the initiation of replication by RPA from other species, suggesting that the interaction of RPA with other replication proteins may be crucial in this process. After unwinding, RPA is believed to both stabilize the unwound DNA and stimulate DNA polymerase α (pol α) and DNA polymerase δ (pol δ) activities, as determined by the elongation of primed DNA templates (13).

In nucleotide excision repair, the requirement for RPA can be bypassed by incising DNA with the E. coli UvrABC enzyme. This observation suggests that RPA is involved in an early stage of UV excision repair (14). Although the role of RPA in repair is not yet well defined, the protein complex cannot be replaced by RPA from other species, indicating that specific interactions between RPA and other repair proteins are involved in the repair process (14).

Xeroderma pigmentosum (XP) is a genetically recessive human disorder. Patients with XP are defective in excision repair of ultraviolet light (UV)-damaged DNA and consequently suffer from a high incidence of skin cancer. At least seven complementation group proteins (XP-A to XP-G) have been identified thus far (15, 16). The XP group A complementing protein (XPAC) is involved in an early stage of nucleotide excision repair and is also a key protein in the recognition of UV-damaged DNA (17–19). The XPAC gene contains a zinc finger motif that is required for XPAC function in repair (20, 21). XPAC was recently shown to interact with rodent excision repair cross-complementing protein 1 (ERCC1) and ERCC4 (XP-F) (22, 23).

In this report, we show that XPAC also interacts with RPA. Further, XPAC inhibits SV40 DNA replication in vitro, and this inhibition can be reversed by the addition of RPA. XPAC inhibited pol α activity in the presence of RPA but did not inhibit this polymerase in RPA’s absence. Taken together, these results indicate that the XPAC-RPA interaction alters RPA’s ability to stimulate pol α activity, which, in turn, results in the inhibition of DNA replication. We discuss how these observations support the hypothesis that the repair and replication functions of RPA are differentially regulated.

**EXPERIMENTAL PROCEDURES**

Proteins, Antibodies, and DNA—SV40 origin-containing circular duplex DNA (pSV013EP, 3.0 kilobases), SV40 T-ag, human DNA pol α-primase, DNA pol δ, PCNA, top1, top2, and RPA were prepared as described previously (24, 25). Human Rad 51 and EBNA1 were the generous gifts of Min S. Park (Los Alamos National Laboratory, NM) and J. Yates (Roswell Park Cancer Center, Buffalo, NY), respectively.
incubating the reaction mixtures for 15 min at 25°C, the DNA-protein (1,200 cpm/fmol), and the indicated amounts of RPA and XPAC. After MgCl₂, 0.5 mM DTT, 10% glycerol, 250 fmol of 5'-32P-labeled (dT)₇₀ was subsequently dried and exposed to x-ray film.

Immediately after the gel run, the gel was dried and exposed to x-ray film.

The gel was blotted, and both bands were excised and subjected to Coomassie Blue staining.

**ssDNA Binding Assay** — The ssDNA binding activity was measured according to the published procedure (13). Reaction mixtures (40 µl) contained 40 µM creatine phosphate-TRis salt (pH 7.7), 1 µg of creatine kinase, 7 mM MgCl₂, 0.5 mM EDTA, 4 mM ATP, 200 µM UTP, GTP, and CTP, 100 µM dTTP, dGTP, and dCTP, 20 µM [α-32P]dATP (specific activity, 20,000 cpm/pmol), 0.8 µg of SV40 T-ag, 0.3 µg of SV40 origin-containing DNA (pSV01A), and various amounts of pol α-primase, topo I, and RPA. In the SV40 polymerase system, various amounts (see Fig. 3B) of PCNA, A2 (RF-C), pol δ, and topo II were also added. The reaction mixtures were incubated for 90 min at 37°C and then stopped with 80 µl of a stop solution containing 20 mM EDTA, 1% SDS, and E. coli tRNA (0.5 mg/ml). Ten percent of the reaction mixture was used to measure the acid-insoluble radioactivity. Replication products in the remaining reaction mixture were analyzed by electrophoresis after separately isolating the reduced DNA in a 12% alkaline agarose gel (40 mM NaOH and 1 mM EDTA) for 12–14 h at 2 V/cm as described previously (28). The gel was subsequently dried and exposed to x-ray film.

DNA pol α and pol δ Assays — DNA pol α and δ activities were assayed as described previously (13) with the following modifications. Reaction mixtures (40 µl) contained 40 µM creatine phosphate-TRis salt, pH 7.7, 1.0 µg of creatine kinase, 7 mM MgCl₂, 1.0 mM ATP, 6 µg of DNA pol α-primase, 20 µM dATP, 33 µM of [α-32P]dCTP (500 cpm/ pmol), 0.1 µg of PCNA, and DNA polymerase, RPA, and XPAC, as indicated. After incubation at 37°C for 30 min, acid-insoluble radioactivity was determined.

**ssDNA Binding Assay** — The ssDNA binding activity was measured according to the published procedure (12, 29, 30). The reaction mixtures (20 µl) contained 50 µg Heps-KOH (pH 7.5), 150 mM NaCl, 1 mM MgCl₂, 0.5 mM EDTA, 10% glycerol, 250 fmol of 5'-32P-labeled (dT)₇₀ (1,200 cpm/fmol), and the indicated amounts of RPA and XPAC. After incubating the reaction mixtures for 15 min at 25°C, the DNA-protein complexes were electrophoretically separated in a 5% polyacrylamide gel in 1 x TBE (89 mM Tris borate, 2 mM EDTA) at 12 V/cm.

**RESULTS**

RPA Interacts with XPAC — In SV40 replication, a defined origin sequence is recognized by the origin-binding protein SV40 T-ag, which interacts with RPA and pol α-primase to form an initiation complex (31–34). This complex is essential for DNA replication because mutant RPA that poorly interacts with SV40 T-ag cannot effectively support DNA replication (12). RPA is also required for nucleotide excision repair, wherein the DNA lesions are specifically recognized by the repair initiator protein, XPAC (19). We reasoned that RPA may function in repair by interacting with XPAC. Accordingly, we examined whether these two proteins interact with each other in vitro. The RPA complex was purified to near homogeneity from insect cells coinfected with recombinant baculoviruses encoding all three subunits (70-, 34-, and 11-kDa subunits) (Fig. 1A; Ref. 25), while bacterially produced histidine-tagged XPAC was induced with isopropyl-1-thio-β-D-galactopyranoside from an XPAC expression vector. As described by others (19), the final stage of XPAC preparation contained a protein doublet, and both bands reacted with antiserum raised against peptides derived from the cDNA of XPAC (Ref. 17; S-HL data not shown). Both RPA and XPAC purified from these expression systems were functionally active in replication and repair, respectively (Refs. 19 and 25; data not shown). An ELISA that successfully detected the interaction of RPA with SV40 T-ag (11, 12) was used to detect the interaction between RPA and XPAC. As with SV40 T-ag, XPAC interacted with RPA (see Fig. 1B).

XPA Inhibits SV40 DNA Replication In Vitro — Having established that XPAC interacts with RPA, we examined the effect of XPAC on SV40 DNA replication in vitro using a reconstituted SV40 replication system. Addition of increasing
amounts of XPAC quantitatively inhibited SV40 DNA replication catalyzed by the monopolymerase system (the monopolymerase system contains SV40 T-ag, DNA pol α-primase complex, topo I, and RPA), whereas buffer alone had no apparent effect (Fig. 2A), indicating that the inhibition was indeed due to XPAC. In the monopolymerase system, as described previously (35), pol α alone can synthesize both the leading (half the length of the plasmid; 1.4–1.6 kilobases) and lagging strands (200–300 nucleotides long), which are shown as two discrete bands (Fig. 2B, lanes 2–6). The synthesis of both strands was inhibited by XPAC. However, since RPA is involved in both the initiation and elongation stages of replication, it is not clear which particular stage XPAC inhibits.

We also examined the effect of XPAC on the dipolymerase system, which contains, in addition to the monopolymerase components, pol δ, PCNA, and activator 1 (RF-C). Again, DNA synthesis was quantitatively inhibited by XPAC (Fig. 3) albeit to a lesser extent than with the monopolymerase system. For example, in the presence of 1.2 μg of XPAC, 82% of the replication activity was inhibited in the monopolymerase system, whereas only 24% was inhibited in the dipolymerase system (Fig. 2A versus Fig. 3A). XPAC affected the sizes of the replication products produced in the SV40 dipolymerase system in that the size of the lagging strand increased as the concentration of XPAC increased. There was also a significant diminution of the leading strand synthesis (Fig. 3B).

XPAC Inhibition Can Be Reversed by the Addition of RPA—If this inhibition targets the function of a particular protein, then reversal of inhibition may simply require the addition of excess targeted protein. The effect of XPAC on SV40 monopolymerase system was effectively reversed by RPA addition but not by the addition of SV40 T-ag, pol α-primase, or topo I (Fig. 4, A and B). This supports the idea that the inhibition of replication by XPAC may result from its interaction with RPA. The size product distribution in the reversed reaction (Fig. 4B, lanes 5–7) is somewhat different from that of the control reaction (Fig. 4B, lane 1), in that the products of leading strand DNA

**Fig. 2.** The effect of XPAC on SV40 monopolymerase replication in vitro. Reaction mixtures (40 μl) contained the pol α-primase complex (0.3 units of pol α and 0.3 units of primase), topo I (1,000 units), 0.3 μg of human RPA, and various amounts of XPAC. With the exception of lane 1, 0.8 μg of SV40 T-ag was included in each reaction. In lanes 3–6, increasing volumes of buffer (25 mM Hepes-KOH, pH 7.8, 25% glycerol, 1 mM DTT, 0.5 mM EDTA, 0.01% Nonidet P-40, and 250 mM KCl) were added, instead of XPAC, to the reactions. Upon completion of the reactions, one-tenth of each reaction mixture was used to measure the TCA-precipitable [α-32P]dAMP incorporated into DNA (A), and the remaining DNA was isolated and analyzed for its size distribution on a 1.2% alkaline agarose gel (B). ssl represents the position to which the single-stranded linear plasmid DNA migrated. n.t., nucleotides.

**Fig. 3.** The effect of XPAC on SV40 dipolymerase replication in vitro. Reaction mixtures (40 μl) contained pol α-primase (0.1 units each), topo I (1,000 units), 0.05 μg of topo II, 0.4 μg of RPA, 0.1 unit of pol δ, 0.4 μg of PCNA, and 0.8 μg of A1. In lanes 2–10, 0.8 μg of SV40 T-ag was included. In lanes 3–6, increasing volumes of buffer were added as described in the legend to Fig. 2. Once the reactions were complete, the reaction mixtures were analyzed for acid-insoluble radioactivity (A) and in a 1.2% alkaline agarose gel (B). ssl represents the position to which the single-stranded linear plasmid DNA migrated. n.t., nucleotides.
synthesis diffused into the smaller products. This can be explained in terms of the RPA concentration in these reactions; excessive amounts of RPA inhibit leading strand synthesis in the monopolymerase system (36). Alternatively, RPA alone may not be able to completely overcome the observed inhibition.

XPAC Does Not Inhibit RPA's ssDNA Binding Activity—It has been shown previously that XPAC preferentially binds to UV-irradiated double-stranded DNA (17, 19). It is possible that XPAC competes with RPA for binding to ssDNA nonspecifically and that this nonspecific interaction leads to the inhibition of DNA replication. Alternatively, XPAC may interact specifically with RPA to produce the inhibitory effect. To distinguish between these possibilities, we examined whether XPAC binds to ssDNA or interferes with RPA's ssDNA binding property. RPA, XPAC, or a mixture of both proteins was incubated with 5'$^{32}$P-labeled (dT)$_{70}$ and analyzed for ssDNA binding activity using a gel mobility shift assay (Fig. 5). As reported previously, RPA binds to ssDNA generating two distinct bands (12, 30). XPAC, however, did not bind to ssDNA in our gel mobility shift assay. Moreover, XPAC did not inhibit RPA's ssDNA binding activity; rather, it stimulated RPA's ssDNA binding activity, supporting the belief that the inhibitory effect of XPAC on SV40 replication results from its interaction with RPA.

XPAC Inhibits the pol $\alpha$ Activity Only in the Presence of RPA—Since RPA stimulates both pol $\alpha$ and pol $\delta$ activities during the elongation stage (13), we examined whether XPAC affects RPA's ability to stimulate either of these polymerases.

**FIG. 4.** The inhibition of SV40 DNA replication by XPAC is reversible by RPA addition. Using the reaction conditions described in the legend to Fig. 2, reversal reactions included 0.4 and 0.8 $\mu$g of SV40 T-ag (lanes 3 and 4, respectively), 0.3, 0.6, and 0.9 $\mu$g of RPA (lanes 5, 6, and 7, respectively), 0.15 and 0.3 units of pol $\alpha$-primase (lanes 8 and 9, respectively), and 500 and 1,000 units of topol (lanes 10 and 11, respectively). After incubation at 37°C for 1 h, the products of the reaction mixtures were analyzed for TCA-precipitable radioactive materials (A), and by 1.2% alkaline agarose gel electrophoresis (B). n.t., nucleotides.

**FIG. 5.** The effect of XPAC on RPA's ssDNA binding activity. Indicated amounts of either human RPA, XPAC, or a mixture of both were combined with 250 fmol of 5'$^{32}$P-labeled (dT)$_{70}$ and incubated for 15 min at 25°C. The protein-DNA complexes were then separated from unbound DNA by 5% polyacrylamide (acylamide:bisacrylamide = 29:1) gel electrophoresis (A). The protein-DNA complex bands were excised and analyzed by liquid scintillation counting (B).

XPAC had no effect on pol $\alpha$ activity in the absence of RPA, but in its presence increasing amounts of XPAC quantitatively inhibited pol $\alpha$ activity (Fig. 6A). This result suggests that the XPAC-RPA interaction prevents RPA from stimulating pol $\alpha$ activity. In contrast, XPAC did not affect pol $\delta$ activity regardless of the presence or absence of RPA (Fig. 6B). Together, these results strongly suggest that the inhibitory effect of XPAC on SV40 replication (Figs. 2 and 3) is likely due to the interaction of XPAC with RPA, which in turn obstructs RPA's stimulation of pol $\alpha$ activity.

**DISCUSSION**

We have examined the interaction of two proteins, XPAC and RPA, that are involved in the early stages of the repair process. We reasoned that because XPAC is a UV-damage recognition protein, RPA may be recruited to damaged DNA sites through its interaction with XPAC. The resulting RPA-XPAC complex might then form multiprotein complexes at the damaged sites to promote recruitment of other repair proteins required for nucleotide excision repair. Recently, XPAC has been shown to interact with ERCC1 (22) or the ERCC1-ERCC4 (XP-F) complex (23), a putative endonuclease complex that is necessary for 5' incision (37). Although the XPAC-ERCC1-ERCC4 complex did not show a damaged site-specific incision (23), it is possible that XPAC, RPA, ERCC1-ERCC4, and other repair proteins, such as the 3' incision endonuclease, XPG (37), form a multi-
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reaction mixtures contained 0.05 units of pol alpha. Insoluble radioactivity was determined. Accurate measurement of the protein complex at the damaged DNA site that is necessary for accurate 3' and 5' incisions.

In addition to its potential role in repair, we found that XPAC inhibited SV40 DNA replication in vitro. This inhibition was reversed by the addition of excess RPA but not by topo I, pol alpha-primase, or SV40 T-ag, indicating that the inhibition and its reversal are physiologically relevant. The inhibition is unlikely to be the result of competition between XPAC and RPA for DNA binding because: (i) two known DNA binding proteins, human Rad51 protein (42) and EBNA1 protein (43), fail to interact with RPA or inhibit the SV40 monoplymerase replication system (data not shown), and (ii) XPAC itself did not show any stable ssDNA binding activity in the gel mobility shift assay; however, it did stimulate RPA's ssDNA binding activity (Fig. 5). RPA binds as a multimer to ssDNA more than 30 nucleotides in length (30). It is therefore possible that the XPAC-RPA interaction stabilizes the binding of RPA to ssDNA binding activity, allowing stable monomeric RPA-ssDNA complexes to form, and leading to the increased amount of RPA-DNA complex that can be seen in Fig. 5. XPAC did not stimulate the ssDNA binding activity of T4 phage ssDNA-binding protein (T4 gene 32), suggesting that the stimulation of RPA's ssDNA binding activity by XPAC occurs through their protein-protein interaction (data not shown). In any event, this result strengthens our belief that the inhibition of replication by XPAC is a result of its interaction with RPA rather than its nonspecific binding to ssDNA.

XPAC binds dsDNA weakly (19); however, this inhibition is unlikely to have resulted from XPAC's interaction with dsDNA because, if this were the case, we would expect to see the same degree of inhibition regardless of the replication system (monopolymerase or dipolymerase) used in the experiments. It is also unlikely that the inhibition resulted from an interaction between XPAC and pol alpha because: (i) XPAC did not interact with pol alpha in our ELISA assay, (ii) addition of excess pol alpha-primase did not reverse the inhibition of replication (Fig. 4), and (iii) XPAC inhibited pol alpha activity in the presence, but not in the absence of RPA. Therefore, the most likely explanation for this inhibition is that XPAC interacts with RPA, altering RPA's ability to stimulate pol alpha.

This belief is further supported by the fact that the inhibitory effect of XPAC is more evident with the monoplymerase system, which relies exclusively on pol alpha activity, than with the dipolymerase system, which contains both pol alpha and pol delta (Fig. 2 versus Fig. 3). Pol delta activity was not affected by XPAC (Fig. 6). In the monoplymerase system, pol alpha is responsible for both leading and lagging strand synthesis; in the dipolymerase system, pol alpha is only partly responsible for lagging strand synthesis, while pol delta is responsible for leading strand synthesis and probably also for part of the lagging strand synthesis (28, 38, 39). On the other hand, we should point out that XPAC had little effect on SV40 replication with HeLa cell cytosolic extracts (data not shown). This lack of inhibition in the crude extracts raises the possibility that our observations are limited to the specific model systems used.

In view of the fact that both RPA and XPAC function in repair, our results would support the hypothesis that the XPAC-RPA complex, once formed, is used in repair rather than in DNA replication. It would be of interest to know whether the XPAC-RPA complex, which is stable enough to be isolated, can still recognize UV-damaged DNA. Since the completion of this work, two articles demonstrating specific interactions between RPA and XPAC have been published (40, 41).

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Fig. 6. The effect of XPAC on RPA's ability to stimulate pol alpha (6A) and pol delta (6B). In addition to the indicated amounts of XPAC, the reaction mixtures contained 0.05 units of pol alpha (A), or 0.05 units of pol delta, 0.2 μg of PCNA, and 0.4 μg of A1 (B). Where indicated, 1.0 μg of RPA was included. After incubation at 37°C for 30 min, acid-precipitable radioactivity was determined.
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