Transcription-positive Cofactor 4 Forms Complexes with HSSB (RPA) on Single-stranded DNA and Influences HSSB-dependent Enzymatic Synthesis of Simian Virus 40 DNA*

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The replication of simian virus 40 (SV40) DNA in vitro requires a trimeric single-stranded DNA (ssDNA)-binding protein called HSSB or RPA. HSSB supports the unwinding of DNA containing the SV40 origin in the presence of the viral-encoded T antigen and is required for the initiation of RNA primer synthesis as well as processive elongation of DNA catalyzed by the DNA polymerase δ holoenzyme. In this report we show that the transcription positive cofactor 4 (PC4), a ssDNA-binding protein, forms complexes with HSSB on ssDNA and markedly affects the replication functions of HSSB. PC4 supports T antigen-catalyzed unwinding of SV40 origins in lieu of HSSB but inhibits both RNA primer synthesis and ssDNA-binding protein δ-catalyzed DNA chain elongation reactions. These inhibitory effects can be reversed by the addition of excess HSSB. Depending on the concentration of HSSB, PC4 can be either inhibitory or activating SV40 DNA replication measured in both monomeric and dipolymerase systems. The possible role of PC4 in the initiation of DNA replication is discussed.

The replication of simian virus 40 (SV40) DNA has been reconstituted in vitro with purified components (1-3). With the exception of the viral-encoded large tumor antigen (T antigen), all of the proteins required for SV40 DNA replication are supplied by the host cell. Thus studies on the enzymatic synthesis of SV40 DNA have served as a useful model of eukaryotic DNA replication.

The trimeric single-stranded DNA binding protein, called HSSB or RPA, is among the best studied of cellular replication factors necessary for SV40 DNA synthesis. HSSB plays important roles in both the initiation and elongation stages of SV40 DNA replication. During initiation, HSSB participates in the SV40 T antigen-catalyzed bidirectional unwinding of duplex DNA around the origin of replication (ori); reviewed in Ref. 4). As a result of direct interactions between T antigen, HSSB and the DNA polymerase (pol) α-primase complex (5-7), pol α-primase is loaded onto the opened SV40 origin and subsequently initiates synthesis of RNA primers (8, 9). Following the initiation reaction, processive DNA elongation on the leading strand and maturation of pre-Okazaki fragments on the lagging strand are catalyzed by the pol δ holoenzyme (pol δ, proliferating cell nuclear antigen (PCNA), and replication factor C (RFC; also called activator 1); Refs. 10-12). HSSB stimulates the RFC-catalyzed ATPase activity which is dependent on both DNA and PCNA (13) and supports elongation of primed DNA templates catalyzed by the pol δ holoenzyme (14).

During the course of HSSB purification from HeLa cell extracts, we observed that a number of preparations contained an 18-kDa protein (relative mobility observed on denaturing polyacrylamide gels) present in stoichiometric amounts with respect to the HSSB polypeptides (p70, p34, and p14). Peptide sequencing of this 18-kDa protein revealed that it is identical to the transcription positive cofactor 4 (PC4; also called p9 precursor), a protein of 127 amino acid residues (15-17). PC4 is a ssDNA-binding protein (17) that mediates interactions between upstream activators and the general transcription machinery (15, 16). HSSB preparations containing PC4, when assayed in SV40 replication reactions, showed altered replication activities compared with those without this protein. These observations prompted us to examine the effects of recombinant PC4, expressed and purified from overproducing Escherichia coli strains, on the HSSB activities that are required for SV40 DNA replication.

**EXPERIMENTAL PROCEDURES**

Preparation of Protein Reagents—The following proteins were prepared as described previously: SV40 T antigen (18), HSSB (19), pol α-primase complex (12), topol (12), PCNA (13), RFC (13), pol δ (20), and PC4 (15).

**ssDNA Binding Assay—Reaction mixtures (10 μl) contained 40 nM creatine phosphate (diTris salt, pH 7.7), 7 mM MgCl2, 0.5 mM DTT, 4 mM ATP, 1.65 μg of bovine serum albumin, 10 fmol of the 5'-32P-labeled 45-nt ssDNA fragment (5' GTT CGG CG7 GGA TCC ACT CCT GTT GCA TCA ACC AAI AAT GTG), and HSSB as indicated. Following a 10-min incubation at 37 °C, antibodies were added to reaction mixtures as indicated. After an additional 10-min incubation at 37 °C, 3 μl of loading buffer (0.5% bromophenol blue, 0.5% xylene cyanol, and 20% Ficoll 4000) was added, and the mixture was electrophoresed through a 3.3% polyacrylamide gel containing 5% glycerol.

**SV40 Origin-dependent Unwinding Assay—Reaction mixture (30 μl) contained 40 nM creatine phosphate (diTris salt, pH 7.7), 7 mM MgCl2, 0.5 mM DTT, 4 mM ATP, 5 μg of bovine serum albumin, 0.5 μg of SV40 T antigen, 0.5 μg of an unlabeled DNA kilobase ladder (Life Technologies, Inc/BRL), 10 fmol of the [32P]-labeled SV40 origin-containing fragment (EcoRI, 311 bp), prepared as described previously (21), and HSSB as indicated. After a 90 min incubation at 37 °C, reactions were terminated by the addition of 5 μl EDTA, 0.5% SDS and 40 μg of E.coli tRNA followed by proteinase K (0.1 mg/ml) digestion for 30 min at 37 °C. The unwound products were separated from the starting mate-

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1 The abbreviations used are: SV40, simian virus 40; PAGE, polyacrylamide gel electrophoresis; DTT, dithiothreitol; ss, single-stranded; ssc, ss circular; T antigen, SV40 large tumor antigen; ori, origin of replication; HSSB, human ssDNA-binding protein, also called RPA; topol, topoisomerase I; DNA polymerase; PCNA, proliferating cell nuclear antigen; RFC, replication factor C, also called activator 1; PC4, positive cofactor 4; nt, nucleotide(s).
Fig. 1. The formation of PC4-HSSB-ssDNA complexes. ssDNA binding assays with HSSB and PC4 were carried out as described under “Experimental procedures.” Reaction mixtures contained 10 fmol of the 5′-32P-labeled 45-nt ssDNA fragment (6,700 cpm/fmol), HSSB, PC4, monoclonal antibody against the p34 subunit of HSSB (0.2 μg of 0–50% ammonium sulfate fraction of the hybridoma supernatant; Ref. 19), and polyclonal antibody against PC4 (0.25 μl), as indicated. DNA-protein complexes were separated by electrophoresis through a 3.5% polyacrylamide gel containing 5% glycerol. Ab refers to the addition of antibodies against either HSSB, used in reactions shown in lanes 4, 7, and 11, or PC4, used in reactions shown in lanes 5, 8, and 12.

Fig. 2. PC4 supports T antigen-catalyzed unwinding of DNA containing the SV40 origin of replication. A, the SV40 ori'' unwinding assay with 10 fmol of the 32P-labeled SV40 origin-containing fragment (3,400 cpm/fmol). T antigen, HSSB, or PC4 was carried out as described under “Experimental Procedures.” Lanes 3–7 contained the following amounts of HSSB: 0.15, 0.45, 0.9, 1.8, and 0.9 μg, respectively. Lanes 8–12 contained 0.1, 0.3, 0.6, 1.2, and 0.6 μg of PC4, respectively. The unwound radiolabeled ssDNA products were separated from the starting materials on a 4% polyacrylamide gel. The positions of the substrate (S) and unwound product (P) are indicated. B, the results shown in A were quantitated using a phosphorimager and plotted.

RESULTS

Formation of PC4-HSSB-ssDNA Complexes—Both HSSB and PC4 are ssDNA-binding proteins (17, 22, 23), and their ability to simultaneously interact with ssDNA was examined utilizing a gel retardation assay as shown in Fig. 1. Incubation of increasing amounts of PC4 with a 32P-labeled ssDNA substrate (45 nt), resulting in a heterogenous population of DNA complexes with reduced mobility following electrophoresis through polyacrylamide gels (lanes 2 and 3). The mobility of these retarded DNA bands was further reduced following addition of antibodies against PC4 (lane 5), but not HSSB (lane 4), confirming the presence of PC4 in these complexes. The size heterogeneity of the PC4-ssDNA complex was most likely due to the association of the ssDNA fragment with variable amounts of PC4.

Incubation of HSSB with the DNA substrate resulted in the formation of a single retarded band (lane 6), the mobility of which was further reduced following addition of monoclonal antibodies recognizing the p34 subunit of HSSB (lane 7), con-
firming the presence of HSSB in this complex. Co-incubation of HSSB and PC4 with the ssDNA fragment yielded complexes that migrated more slowly than either the HSSB DNA or PC4 DNA complexes (lanes 9 and 10). HSSB and PC4 were both present in these DNA-protein complexes, since the migration of these complexes was retarded by the addition of antibodies recognizing either HSSB or PC4 (lanes 11 and 12). Thus HSSB and PC4 were capable of simultaneously interacting with ssDNA.

PC4 Supports T Antigen-catalyzed Unwinding of SV40 Origin Containing Duplex DNA—In the presence of ATP, HSSB supports T antigen-dependent unwinding of duplex DNA containing SV40 ori. We examined whether PC4, a nonreplicative ssDNA-binding protein, was capable of substituting for HSSB in SV40 ori DNA unwinding (Fig. 2A). This assay measured the production of unwound ssDNA from a 32P-labeled duplex ori DNA fragment in the presence of T antigen, ATP, and either HSSB (lanes 3–7) or PC4 (lanes 8–12). Quantitation of the results (Fig. 2B) demonstrated that PC4 supported the T antigen-dependent unwinding reaction to a similar extent as HSSB.

PC4 Inhibits DNA Primase-catalyzed Synthesis of Oligoribonucleotides—In the SV40 replication system, RNA primers on both leading and lagging strands are synthesized by the pol α-primase complex in the presence of ori DNA, HSSB, and topo I. No other SSB can substitute for HSSB in this reaction (8). We tested whether PC4, which was capable of forming PC4-HSSB-ssDNA complexes and supporting T antigen-catalyzed unwinding, was able to interfere with RNA primer synthesis. As shown in Fig. 3, the synthesis of oligoribonucleotides in the presence of [α-32P]JUTP (10–16 nt in length) was dependent upon the addition of T antigen and HSSB, since omission of either of these from the reaction resulted in no primer synthesis (lanes 1 and 6).

PC4 could not substitute for HSSB in this reaction (lane 7) and when added in the presence of HSSB, markedly inhibited RNA primer synthesis (lane 8). This inhibition was reversed partially by the addition of excess HSSB (lanes 9–11), suggesting that PC4 inhibited this reaction by competing with HSSB.
PC4 Regulates HSSB-dependent SV40 DNA Replication

Figure 6. Effects of PC4 on SV40 DNA replication in the dipolymerase system. SV40 DNA replication in the dipolymerase system was carried out as described under "Experimental Procedures." The 32P-labeled DNA replication products were separated by electroforeisis through a 1.5% alkaline agarose gel. 32P-Labeled size markers (nt) are shown at the right side of the gel. The extent of dCMP Incorporation is indicated under each lane.

Table 1
Summary of effects of PC4 on activities intrinsic to HSSB that are required for replication

| HSSB activity | Influence of PC4 |
|---------------|------------------|
| ssDNA binding | Formed HSSB-PC4-ssDNA complexes |
| Unwinding of SV40 ori by T antigen | Replaced HSSB for this activity |
| RNA primer synthesis | Inhibition |
| DNA elongation by pol δ | Inhibition |
| SV40 DNA replication | Inhibition |
| Low HSSB (4-10 µg/ml) | Inhibition |
| High HSSB (80-260 µg/ml) | Activation |

DNA replication, which is catalyzed by the pol δ holoenzyme. To assess the influence of PC4 on the HSSB-dependent pol δ-catalyzed reaction, a singly primed DNA complex was carried out (Fig. 4). In this reaction, template DNA was incubated with the pol δ holoenzyme (pol δ, PCNA, and RFC) and HSSB in the presence of dNTPs, resulting in the incorporation of [32P]dCMP into full-length DNA (lanes 2-4). In the absence of HSSB (lane 1) or PCNA (lane 5), little DNA synthesis was detected. PC4 did not substitute for HSSB in the elongation reaction (lane 6).

The addition of PC4 inhibited this elongation reaction (lane 7). However, in the presence of excess HSSB, the PC4-dependent inhibition was markedly decreased (lanes 8 and 9), suggesting that PC4 abolished DNA elongation activity by specifically inhibiting the function of HSSB.

Effects of PC4 on SV40 DNA Replication Utilizing the Monopolymerase System—SV40 DNA replication can be assayed using both the mono- and dipolymerase systems (12). The monopolymerase system requires ori DNA, HSSB, topo I, and relatively high levels of the pol α-prime complex which catalyzes both leading and lagging strand DNA synthesis in the presence of dNTPs. In this system replication products derived from lagging strand DNA synthesis can be readily separated from those of the leading strand by alkaline agarose gel electrophoresis. In complete reactions containing HSSB at 3.8 or 19 µg/ml (Fig. 5, lanes 2 and 6), two discrete products were observed, centered at -75 nt (lagging strand) and -1,600 nt (leading strand). When HSSB was added at high levels (89 and 260 µg/ml), the reaction was inhibited (lanes 7 and 8). This inhibition resulted from decreased RNA primer synthesis and leading strand DNA elongation in the presence of high levels of HSSB, as reported previously (Refs. 12 and 24; also see Fig. 3). The reasons for this effect are presently unknown; however, it is conceivable that excess HSSB may "squelch" T antigen or/and the pol α-prime complex resulting in the formation of inactive complexes.

The influence of PC4 on the monopolymerase system was dependent upon the concentration of HSSB. In the presence of 3.8 µg/ml of HSSB, the addition of a low level of PC4 (0.8 µg/ml) resulted in a 35% stimulation of leading strand DNA synthesis (lane 3) (as quantitated by phosphorimager analyses). Although the level of Okazaki fragment synthesis (100-500 nt) remained unchanged, the size of lagging strands was markedly increased. In contrast, the addition of higher levels of PC4 inhibited both lagging and leading strand DNA synthesis (lanes 4 and 5). This inhibition may result from the ability of PC4 to inhibit primase activity as demonstrated in Fig. 3. Thus, low levels of PC4, which partially inhibit RNA primer synthesis, probably result in an increase in the distance between RNA primers on the lagging strand. Elongation of these RNA primers by pol α results in longer DNA products as shown in lane 3. The presence of higher levels of PC4 completely inhibited primase activity and thus no replication ensued.

In the presence of high levels of HSSB (89 and 260 µg/ml), replication was inhibited (lanes 7 and 8), and the addition of PC4 (4 µg/ml) markedly stimulated the reaction (lanes 10 and 11). Quantitation of these results by phosphorimager analyses indicated that in the presence of 89 µg/ml of HSSB, the addition of PC4 (4 µg/ml) increased leading and lagging strand DNA synthesis by 2.8- and 1.9-fold, respectively (compare lanes 7 and 10). In the presence of 260 µg/ml HSSB, the addition of the PC4 (4 µg/ml) increased leading and lagging strand DNA synthesis by 4.5- and 3.3-fold, respectively (compare lanes 8 and 11). These observations demonstrated that PC4 was able to (i) overcome the inhibitory effects of high levels of HSSB in the monopolymerase system, (ii) activate replication to levels higher than those observed with low ("optimal") concentrations of HSSB, and (iii) the PC4-mediated stimulatory effects were more pronounced as the concentration of HSSB was increased (compare lane 4 with lanes 9-11).

Effects of PC4 on SV40 DNA Replication Utilizing the Dipolymerase System—Processive leading strand DNA synthesis and maturation of Okazaki fragments during SV40 replication
are catalyzed by the pol δ holoenzyme. The dipolymerase system contains ori+ DNA, low levels of the pol α-primase complex, HSSB, top1, and the pol δ holoenzyme in the presence of dNTPs. Fig. 6 shows the influence of PC4 on the dipolymerase replication reaction. Products labeled with [32P]dCMP that formed in the replication reaction were analyzed by alkaline agarose gel electrophoresis.

In the absence of the pol δ holoenzyme, only small Okazaki fragments (~75 nt long) were formed due to the action of limiting amounts of the pol α-primase complex (lane 1). Addition of increasing amounts of HSSB inhibited this reaction (lanes 2 and 3), consistent with previous observations (Fig. 5). In the presence of the pol δ holoenzyme, a heterogeneous population of products (150–3,000 nt) was synthesized (lane 4). This reaction required PCNA (lane 5), T antigen (lane 6), and HSSB (lane 16). High levels of HSSB (138 μg/ml) virtually abolished the dipolymerase replication reaction (lane 8).

As observed in the monopolymerase system, the influence of PC4 on the dipolymerase reaction was dependent upon the amount of HSSB added. In the presence of a low level of HSSB (10 μg/ml), the addition of a low level of PC4 (1.9 μg/ml) slightly stimulated the replication reaction (compare lanes 4 and 9). Under these conditions, the synthesis of both long (1,018–3,054 nt) and short DNA products (344–1,018 nt) increased 62 and 49%, respectively (quantitated by phosphorimager analysis). In the presence of high levels of PC4 (4 μg/ml), replication was inhibited 70% (compare lanes 4 and 12).

In reactions containing higher concentrations of HSSB (25 μg/ml), replication was slightly stimulated by the addition of a low level of PC4 (1.9 μg/ml) (compare lanes 7 and 10). At this concentration of HSSB, the addition of a high level of PC4 (4 μg/ml) reduced replication by 10% (lane 13).

In the presence of a very high level of HSSB (138 μg/ml), replication was nearly abolished (lane 8), but the addition of increasing amounts of PC4 (to 1.9 and 4 μg/ml) reversed this inhibition (lanes 11 and 14) in a PCNA-dependent reaction (lane 15). This indicates that the extensive DNA synthesis observed in the presence of PC4 (lane 14) was catalyzed by the pol δ holoenzyme.

**DISCUSSION**

The in vitro replication of SV40 DNA can be regulated by a variety of proteins that either directly target T antigen, such as cyclin-dependent cdk2 kinase (25), phosphatase 2A (26), p53 (27), and p107 (28), or interact with PCNA, such as p21cip (29, 30). These studies have contributed to our understanding of the cellular controls governing DNA replication. The data presented in this report demonstrated that PC4, a ssDNA binding protein that functions as a transcription co-activator, can influence several activities associated with HSSB that are required for replication (see Table I for a summary). Depending on the concentration of HSSB used, PC4 can either inhibit or activate SV40 DNA replication as assayed in both the monomeric and dipolymerase systems.

The binding of a replication initiator protein, such as T antigen, to its origin results in localized melting of duplex DNA (4). The resulting ssDNA region must be stabilized by a ssDNA-binding protein in order for T antigen, a replicative helicase, to further catalyze bidirectional unwinding. Various prokaryotic and virus-encoded replicative ssDNA-binding proteins are capable of supporting this unwinding reaction in place of HSSB (reviewed in Ref. 4). However, subsequent RNA primer synthesis, catalyzed by the pol α-primase complex, can only occur in the presence of HSSB (8). Thus, binding of nonreplicative ssDNA-binding proteins such as PC4, to unwound ssDNA regions, may have profound effects on the initiation of chromosomal DNA replication.

Based on studies presented in this report we propose a working model (Fig. 7) to explain the effect of PC4 on the initiation of SV40 DNA replication. In the presence of limiting concentrations of HSSB, T antigen unwinds DNA at the origin and then assembles a preinitiation complex with HSSB and pol α-primase due to its direct interaction with these proteins (5–7), resulting in the synthesis of RNA primers (A). Excess HSSB inhibits initiation presumably by "squeezing" T antigen (B, diagram a) and/or pol α-primase (B, diagram b), respectively.

PC4 supports T antigen-catalyzed unwinding in place of HSSB (see Fig. 2) and may increase the percentage of duplex DNA molecules unwound around the SV40 origin (illustrated as two origins opened in C as opposed to one origin opened in Fig. 7A). However, in the presence of low levels of HSSB, this effect may decrease the amount and availability of HSSB in the vicinity of T antigen and reduce the loading of the pol α-primase complex at the origin. In contrast, when high levels of HSSB are present, the PC4-mediated increase of unwound ssDNA regions may contribute to the efficient binding of HSSB (Fig. 7D). As a result, the HSSB-mediated "squeezing" of T antigen and the pol α-primase complex is markedly reduced favoring the formation of active preinitiation complexes. Under these conditions, high concentrations of HSSB suppress the inhibitory effects of PC4 on RNA primer synthesis and pol α-catalyzed DNA elongation (see Figs. 3 and 4). These combined actions may account for the highly efficient DNA replication observed.

As shown in Fig. 1, PC4 was capable of forming complexes with HSSB on a single-stranded DNA fragment. The direct association between HSSB and PC4 was not detected by co-immunoprecipitation experiments (data not shown). However,
it is possible that HSSB at high concentrations transiently interacts with PC4, preventing the HSSB-mediated squelching of both T antigen and the pol α-primase complex.

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