Functional Interaction between p/CAF and Human Papillomavirus E2 Protein*

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Daeyeop Lee, Sun Gwan Hwang, Jiyun Kim, and Joonho Choe‡
From the Department of Biological Sciences, Korea Advanced Institute of Science and Technology, Daejeon 305-701, Korea

p300/CREB-binding protein-associated factor (p/CAF), a transcriptional co-activator, interacts with co-activator p300/CBP and acidic transcription factors. p/CAF mediates transcriptional activation by acetylating nucleosomal histones and cellular factors. Previously we reported that CBP binds to human papillomavirus E2 and activates E2-dependent transcription (Lee, D., Lee, B., Kim, J., Kim, D. W., and Choe, J. (2000) J. Biol. Chem. 275, 7045–7051). Here we show that p/CAF binds to the human papillomavirus E2 protein in vivo and in vitro and activates E2-dependent transcription. CBP along with p/CAF synergistically activates E2-dependent transcription. In addition, the histone acetylase activity of p/CAF is required for efficient activation of E2 transcriptional activity. These results suggest that p/CAF is a transcriptional co-activator of the human papillomavirus E2 protein.

Transcriptional co-activators, recruited by sequence-specific transcription factors, enhance transcriptional activation of target genes via interaction with chromatin remodeling complexes and RNA polymerase II holoenzyme complex. p300/CREB-binding protein (CBP)1-associated factor (p/CAF) was originally identified as a p300/CBP-binding protein by virtue of its sequence homology to a yeast histone acetyltransferase (HAT), yGCN5 (1). pCAF has an HAT activity and transcriptional activation activity (1, 2). Its ability to stimulate transcription is independent of p300/CBP, but is dependent on the intrinsic HAT activity of p/CAF (3). pCAF directly interacts with the transcriptional co-activators such as p300/CBP (1), steroid receptor co-activator 1 (4), and activator of the thyroid and retinoic acid receptor (5) as well as various activators including nuclear hormone receptors (2), MyoD (3), and interferon regulatory factor family (6). Recently, it is known that p/CAF can form a complex with more than 20 associated polypeptides (7). These results implicate that the p/CAF complex is recruited to a wide range of promoters via multiple protein-protein interactions.

The papillomavirus E2 open reading frame encodes several proteins that bind to the consensus E2-binding site (E2BS), ACNN,GGT, and regulate viral transcription and DNA replication (8, 9). Full-length E2 protein can support viral transcription and DNA replication, whereas alternatively spliced forms of the E2 protein that lack the amino-terminal domain act as repressors of transcription (10, 11). Analysis of the amino acid sequences of various E2 proteins shows that the NH2-terminal and COOH-terminal regions are relatively well conserved (8, 9). A transcription activating domain is encoded by the conserved NH2-terminal region and a DNA-binding domain is encoded by the conserved COOH-terminal region. The activation domain of bovine papillomavirus type 1 E2 contains two regions within the first 85 amino acids that are predicted to form acidic amphipathic helices (12). It has been proposed that the E2 amphipathic helices might be responsible for interaction with host transcriptional modulators (12, 13). The COOH terminus of E2 interacts with several proteins such as E1, TATA-binding protein, transcription factor IIB, and p53, suggesting that the COOH terminus of E2 also contains the receptor site for communicating with other regulatory proteins (14–17). These facts demonstrate that several co-activators interact with E2 and will modulate E2-dependent transcription.

In this study, we show that (i) human papillomavirus (HPV) E2 interacts with p/CAF, (ii) this interaction requires residues 1–390 in the NH2 terminus of p/CAF, (iii) p/CAF strongly activates E2-dependent transcription, and (iv) p/CAF appears to be recruited to the E2-dependent promoter to the hyperacetylate promoter region in vivo. Our data showed that one mechanism by which transcriptional activation of HPV-18 E2 protein is through protein-protein interaction between E2 and p/CAF.

EXPERIMENTAL PROCEDURES

Plasmids—pCG-18E2, pEBG-18E2, pCDNA3-mCBP, and p2x2x-E2BS-Luc were previously described (18) and p/CAF expression vector (pCX-p/CAF) and anti-p/CAF polyclonal antibody were presented from Dr. Y. Nakatani. pGEX4T-18E2N (amino acids 1–261 of the HPV-18 E2) and pGEX4T-18E2C (amino acids 261–365 of HPV-18 E2) were constructed by polymerase chain reaction (PCR) amplification using appropriate primers. Green fluorescent protein (GFP)-E2 expression vectors were engineered by PCR using appropriate primers. pCDNA3-p/CAF(1–390) and pCDNA3-p/CAF(352–658) were cloned into pCDNA3 using PCR products of amino acids 1–390 and 352–658 of p/CAF, respectively. Several glutathione S-transferase (GST)-fused p/CAF proteins were cloned into pGEX4T-1 by the PCR method using appropriate primers. The pFR-Luc and pM plasmids were purchased from CLONTECH.

Cells, Transfection, and Reporter Assay—Human embryonic kidney cell 293T and human cervical cancer cell C33A were maintained in Dulbecco's modified Eagle's medium supplemented with 10% fetal bovine serum. Twenty-four hours before transfection, 3 x 105 cells were plated in 60-mm plates. Transfections were performed either by the standard calcium phosphate method (19) or by LipofectAMINE (Invitro-
The transfected plasmids were prepared by the Qiagen procedure (Qiagen, Hilden, Germany), and the total amount of transfected DNA was adjusted with pCDNA3 or blank plasmid DNA. Equal amounts of cell lysates were employed for the detection of luciferase (Luc) activity. Luc activity was normalized by protein concentration or galactosidase activity using Luminescent β-galactosidase detection kit II from CLONTECH Laboratories Inc. (Palo Alto, CA).

**GST Pull-down Assays**—Radiolabeled, *in vitro* translated proteins were incubated with GST fusion protein in T buffer (50 mM Tris-HCl (pH 7.5), 100 mM NaCl, 5 mM EDTA, 2.5 mM dithiothreitol, 0.7 mg/ml bovine serum albumin, 0.5% Nonidet P-40). After incubation at room temperature for 20 min, glutathione-Sepharose beads were added, and this mixture was incubated on a rotating machine (Nutator) for 1 h at room temperature. The beads were washed four times with T buffer, 5 × loading dye (60 mM Tris-HCl (pH 6.8), 25% glycerol, 2% sodium dodecyl sulfate, 14.4 mM 2-mercaptoethanol, 0.5% bromphenol blue) was added, and the proteins were subjected to SDS-PAGE.

**Cell Culture and Transfection**—Thirty-six hours after transfection,
the cells were harvested and lysed to yield the cell extract using EBC buffer (50 mM Tris-HCl (pH 7.5), 120 mM NaCl, 0.5% Nonidet P-40, 100 mM NaF, 200 μM sodium orthovanadate, 1 mM dithiothreitol, 1 mM phenylmethylsulfonyl fluoride). Incubation of the transfected cell extracts with GST or protein G (detecting for FLAG antibody) resin resulted in the co-precipitation of GST-18E2 and FLAG-p/CAF. The resulting precipitates were washed, and the proteins were resolved by SDS-PAGE. The GST-18E2 fusion protein and FLAG-p/CAF were detected by Western blotting using anti-GST and anti-FLAG antibodies from Sigma, respectively.

Immunofluorescence—293T cells were cultured on glass coverslips and transfected with calcium precipitation. Twenty-four hours later, the cells were washed with phosphate-buffered saline twice and fixed in 3.7% formaldehyde in phosphate-buffered saline for 20 min. The cell membrane was permeabilized by treatment with 1% Triton X-100 for 30 min. The cells were washed with phosphate-buffered saline, and non-specific antibody binding was blocked with 1% bovine serum albumin. The cells were treated with mouse anti-FLAG monoclonal antibody (Sigma) or anti-p/CAF polyclonal antibody at a dilution 1:1000 (anti-FLAG) or 1:200 (anti-p/CAF) for 2 h. After washing with phosphate-buffered saline, the cells were stained with donkey anti-mouse TRITC 488 and goat anti-rabbit TRITC at a dilution 1:2500 for 2 h. The cells were washed, treated with prolonged mounting media, and the proteins were visualized using an immunofluorescence microscope (Zeiss).

Micrococcal Nuclease Assay—Micrococcal nuclease digestions (0–0.64 units, Sigma N5386) were performed on purified nuclei for 20 min at room temperature in Mnase digestion buffer (60 mM KCl, 15 mM NaCl, 15 mM Tris-HCl (pH 7.4), 0.25 mM sucrose, 1 mM CaCl₂, 0.5 mM dithiothreitol). The reaction was terminated and DNA was extracted using phenol extraction. After proteinase K treatment and ethanol precipitation, DNA was treated with RNase A.

Mutagenesis—p/CAF L606A was made using the QuickChange site-directed mutagenesis Stratagene kit (Stratagen, San Diego, CA) according to the manufacturer’s instructions. Mutants was identified by automated DNA sequencing.

Chromatin Immunoprecipitation (ChIP) Assays—ChIP assays were performed essentially as described in the Upstate Biotechnology protocol. Briefly, a 10-cm dish of 50% confluent 293T cells was transfected with 2 μg of p2x2xE2BS-Luc reporter plasmid, 2 μg of pCX-p/CAF, and/or 2 μg of pCG-18E2 plasmid. Twenty-four hours after transfection, cells were cross-linked and treated as per the protocol. Twenty-four hours later, cells were cross-linked and treated as per the protocol. About 1 μg of each indicated antibody was used (anti-acetylated H3 histone). Precipitated DNA was resuspended in 50 μl of water. To detect the precipitated plasmid sequence, 1–5 μl of DNA was used in a 100 μl, 22–30 cycles PCR with primers (for p2x2xE2BS-Luc, Luc5 (5'-ATGGAAGACGCCAAAAACAT-3') and Luc3 (5'-CATAGCTCTTGCAACCGAA-3')).

RESULTS

Interactions of p/CAF with HPV-18 E2—We previously reported that CBP interacts with HPV-18 E2 (18). Because p/CAF has a co-activator function independent of p300/CRBP, we attempted to decipher whether p/CAF also functionally interacts with HPV-18 E2. To determine whether p/CAF binds to HPV-18 E2 in vivo, we co-transfected GST-fused HPV-18 E2 and FLAG-tagged p/CAF expression vectors into 293T cells. As shown in Fig. 1A, FLAG-p/CAF is only detected in GST resin

![Fig. 2. HPV-18 E2 binds to p/CAF in vitro. A, schematic representation of recombinant GST-18E2 fusion proteins used in this study. GST pull down assays between GST-E2 fusion proteins and p/CAF. B, top, equal amounts of GST and various GST-E2 proteins were incubated with 35S-labeled in vitro translated p/CAF and each sample was precipitated with GST-resin. The resin-bound protein complex was resolved by SDS-PAGE. p/CAF was visualized by autoradiography. Bottom, shown are the GST-E2 fusion proteins used in GST pull down assays. Asterisk (*) indicates GST fusion proteins.](http://www.jbc.org/content/6485/1/6485/F2)

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precipitates when co-transfected with GST-E2. FLAG-p/CAF did not co-precipitate with GST along with FLAG-p/CAF or GST-E2 alone, indicating that p/CAF binds to HPV-18 E2 in vivo. Similarly, GST-E2 is only detectable in protein G (for detecting FLAG antibody) precipitates when co-transfected with FLAG-p/CAF (Fig. 1B). As a negative control, we used FLAG-tagged HPV-11 E7. Western analysis showed that GST, GST-E2, FLAG-E7, and FLAG-p/CAF were properly expressed in the transfected 293T cells. These results also showed that p/CAF binds to HPV-18 E2 in mammalian cells. The existence of E2-p/CAF complex was further confirmed by the intracellular localization of p/CAF and HPV E2 using confocal microscopy (Fig. 1C). GFP-E2 brought FLAG-p/CAF or endogenous p/CAF into nuclear dots, indicating that p/CAF and HPV-18 E2 proteins are co-localized in nucleus.

**HPV-18 E2 and p/CAF Interact in Vitro**—To show that HPV-18 E2 binds to p/CAF in vitro, we performed GST pull down assays using recombinant GST fusion proteins of HPV-18 E2. The schematic representation of each recombinant GST-E2 proteins is shown in Fig. 2A. GST pull down assays demonstrated that p/CAF bound to both the transactivation domain and DNA-binding domain of E2 (Fig. 2B). To confirm that GST pull down assays were specific, we carried out the same assay using recombinant GST proteins and in vitro translated Luc under the same condition as a negative control. Previous reports (18, 20) demonstrated that p300/CBP binds to the NH2 terminus of HPV-18 E2. Our data showed that transactivation domain and DNA-binding domain of E2 interacts with p/CAF in vitro.

To define the HPV-18 E2-binding domain within p/CAF, GST pull down assays were carried out using recombinant GST fusion proteins of p/CAF (Fig. 3A). As shown in Fig. 3B, the NH2 terminus of p/CAF bound to the full-length HPV-18 E2 in vitro. In vitro translated E2 was not bound to GST alone, GST-p/CAF-(658–832), and GST-p/CAF-(352–658).

**p/CAF Synergistically Stimulate E2-mediated Transcription**—E2 binds to E2BS and activates or represses cognate binding site-dependent transcription (11). Because p/CAF can activate several transcription factors (3, 5, 6), we carried out a transient reporter assay to test the role of p/CAF in E2-dependent transcription using E2 expression (pCG-18E2) and E2-dependent reporter (p2x2xE2BS-Luc) plasmids. Co-transfection of pCG-18E2 and the p2x2xE2BS-Luc reporter was performed in the presence or absence of pCX-p/CAF and pCDNA3-mCBP. Twenty-four hours after transfection, cells were lysed using a Reporter lysis buffer (Promega). Equal amounts of cell lysates were employed for the detection of Luc activities. We added 0.5 μg of β-galactosidase expression vector to each transfectant as an internal control. Fig. 4A showed that p/CAF activated the E2-dependent transcription (maximum 7-fold), and CBP and p/CAF can further boost this high level of activity an additional 2–3-fold. Co-transfection of CBP and p/CAF expression plasmids significantly augmented E2-dependent transcription by about 8.4-fold. These results showed that p/CAF and CBP synergistically activate E2-dependent transcription. This synergy is believed to reflect a cooperative recruitment of the different co-activators (such as p300/CBP and p/CAF) by E2. Fig. 4B showed that p/CAF did not affect basal E2-dependent transcription of a reporter plasmid (p2x2xE2BS-Luc). Since HPV-18 E2 binds to the NH2 terminus of p/CAF in vitro (Fig. 3), we tested whether the ectopic expression of the NH2 terminus of p/CAF (pCDNA3-p/CAF-(1–390)) had an effect on E2-dependent transcription in C33A cells. As shown in Fig. 4C, the NH2 terminus of p/CAF repressed E2-dependent transcription in a dose-dependent manner, while the HAT domain of p/CAF did not affect the E2-dependent transcription.

The E2 proteins from various HPV strains were tested in this assay. The E2 open reading frames of HPV-6b, -11, and -16 were in vitro translated using a TNT-coupled reticulocyte system (Promega). Using the GST-p/CAF-(1–390), pull down assays were carried out (Fig. 5A). These results showed that...
other types of HPV E2 proteins also bind to GST-p/CAF in vitro. Next, we tested whether the transcriptional activity of various HPV E2s was stimulated by p/CAF. As expected, we observed that p/CAF stimulated HPV E2-dependent promoter (Fig. 5B). HPV strains fall into two categories: a high-risk group (HPV-16 and -18) and a low-risk group (HPV-6 and -11) for the development of cervical cancer. E2 from the low-risk group of HPV showed a weak stimulatory effect on E2-dependent transcription, as compared with that of E2 from the high-risk group. From these results, we concluded that p/CAF has a universal property that stimulates transcriptional activation function of various HPV E2.

The HAT Activity of p/CAF Is Necessary for E2-dependent Transcription—To test whether the HAT activity of p/CAF is required for E2-dependent transcription, we constructed pCAF(L606A), which lost the intrinsic HAT activity of p/CAF (21). This pCAF mutant did not acetylate histone proteins (data not shown). We carried out transient reporter assay using E2 expression and E2-dependent reporter plasmids. Co-transfection of pCG-18E2 and the p2x2xE2BS-Luc reporter was performed in the presence or absence of pCX-p/CAF and pCX-pCAF(L606A). As shown in Fig. 6A, the wild type pCAF activated E2-dependent transcription by 2.3–5.8-fold. pCAF(L606A), however, did not augment and rather repressed E2-dependent transcription. To confirm whether p/CAF and mutant p/CAF modulated E2 expression levels, we performed Western blot and Northern blot. As shown in Fig. 6A, the amounts of E2 in the presence of wild type p/CAF expression plasmid was almost the same as that observed without the p/CAF expression plasmid. Our data imply that transactivator E2 recruits HATs into its cognate promoter to hyperacetylate its promoter region, resulting in activation of E2-dependent promoter.

Because E2 required HAT activity of p/CAF for activating its transcriptional activation, we tested whether E2 recruits p/CAF to its promoter region for inducing hyperacetylation. We examined the acetylation status of p2x2xE2BS-Luc promoter...
using antibody specific for acetylated histone H3 and ChIP assay from Upstate Biotechnology (Lake Placid, NY). We co-transfected p/CAF, p/CAF(L606A), and p2x2xE2BS-Luc in the presence or absence of E2 and recovered DNA by ChIP. Semi-quantitative PCR showed that E2-dependent promoter was hyperacetylated (Fig. 6B). Without co-transfection of E2, less p2x2xE2BS-Luc was precipitated. When we co-transfected p/CAF(L606A) with E2 expression plasmid, the histone H3 in p2x2xE2BS-Luc was not hyperacetylated. We performed in vitro acetylation assay using recombinant E2 protein and p/CAF did not acetylate E2 protein while p/CAF acetylates histone or E2F sufficiently under our experimental condition (data not shown). To address whether transfected DNA might assemble into a nucleosome structure, we performed micrococcal nuclease digestion of isolated nuclei from cells transiently transfected with combination of p2x2xE2BS-Luc and E2 expression vector (Fig. 6C). Nuclei were subjected to digestion with increasing amounts of micrococcal nuclease (0–0.64 unit).
for 20 min at room temperature. Bulk DNA was isolated and separated on a 1.8% agarose gel (Fig. 6C, left panel). The isolated DNA was subjected to Southern blot analysis and hybridization with luciferase gene fragment (Fig. 6C, right panel). Mono- and dinucleosomes can be detected, consistent with previous results (22). From these results, we concluded that the E2-dependent promoter is hyperacetylated by HATs and p/CAF appears to activate E2-dependent promoter by acetylating promoter region in vivo.

**DISCUSSION**

It has been well known that p300/CREB and p/CAF form a coactivator complex to facilitate transcription (23). p/CAF, which associates with viral acidic transcription factors such as Epstein-Barr virus EBNA2 and Herpes simplex virus VP16, binds to p300/CREB and potentiates viral promoter and host promoters through cooperatively association with other co-activators (24). However, Reid et al. (21) showed that p/CAF stimulates transcription in yeast, which does not contain p300/CREB. They also showed that a p/CAF deletion mutant, which does not contain the binding region for CREB, augments Rous sarcoma virus long control region-dependent transcription in mammalian cells. These results suggest that p/CAF has an independent role in transcriptional activation from CREB/p300. Previously we reported that CBP binds to human papillomavirus (HPV) E2 and activates E2-dependent transcription (18). CBP/P1541A, a HAT-negative CREB mutant, did not stimulate E2-dependent transcription as the wild type CBP. In this report, we showed that p/CAF and CREB activates E2-dependent promoter synergistically. CBP/P1541A retains the ability to increase the E2-dependent transcription marginally. This residual effect suggests that HAT activity can be provided by other CREB-associated proteins or other factors. In this paper, we demonstrated that p/CAF/L606A, an HAT-negative p/CAF mutant, is not able to stimulate E2-dependent transcription and it shows a dominant negative effect on E2-dependent promoter, indicating the possibility that p/CAF may be the major HAT for E2-dependent transcription. Our preliminary data showed that E2 was not acetylated by p/CAF and CREB (data not shown). From these results, we speculated that the HAT activities of CREB and p/CAF are related to the acetylation status of promoter region. p/CAF and p300/CREB have been shown to acetylate nucleosome histones in vitro (1, 7, 25). The post-translational modifications such as acetylation and phosphorylation are thought to facilitate or block transcription by altering the chromatin structure. p/CAF and p300/CREB have also been shown to acetylate the transcription factors (26–30), and the transcriptionally active tumor-suppressor protein p53 has been shown to undergo functionally relevant acetylation by p300 and p/CAF (31, 32). Because the augment of E2-dependent transcription is reduced when the HAT function of p/CAF is disrupted, it seems likely that the effect of p/CAF on E2-mediated transcription also involves acetylation of histones or other substrates. Our ChIP assay shows that E2-dependent promoter is hyperacetylated by E2, which binds to E2BS. Thus, E2 seems to recruit HATs into its cognate promoter region in vivo and the HAT activities are important for efficient stimulation of E2-dependent promoter. In this study, we define that co-activator p/CAF specifically binds to HPV E2 and stimulates E2-dependent transcription in vivo. These findings are consistent with the notion that E2 is modulated by many cellular factors and these protein-protein interactions may provide the various functions in host cells such as apoptosis and transcriptional or replication modulation of HPV E2 protein.

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