The Viral Oncogene Human Papillomavirus E7 Deregulates Transcriptional Silencing by Brm-related Gene 1 via Molecular Interactions*

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BRG-1, a component of the human SWI/SNF complex, either activates or represses cellular promoters by modulating chromatin structure via the formation of a multiple polypeptide complex. Human papillomavirus E7 binds and destabilizes pRb, resulting in the blockage of G1 arrest in the cell cycle. We show here that the high-risk human papillomavirus E7 protein group binds BRG-1 and modulates repression of the c-fos promoter mediated by this protein. In addition, both wild-type and Rb binding-defective E7 proteins abolish flat cell formation by BRG-1 in SW13 cells, whereas E7 COOH-terminal mutants do not affect this process. BRG-1-triggered repression of the c-fos promoter is sensitive to trichostatin A. We further establish that BRG-1 contains an activation domain and a trichostatin A-sensitive repression domain. These results collectively suggest that the viral oncogene E7 targets both pRb and BRG-1 via protein-protein interactions, resulting in the deregulation of host cell cycle control.

Oncogenic transformation is often caused by the aberrant expression of key genes that regulate growth properties of the cell. Many transcription factors possess DNA binding properties to modulate cellular gene expression. These DNA-binding proteins frequently communicate with other cellular co-factors, such as co-activators and co-repressors, and regulate target gene expression through modification of the chromatin structure (1).

Brm-related gene 1 (BRG-1), a component of the human SWI/SNF complex, is a homolog of Drosophila melanogaster brahma and Saccharomyces cerevisiae SNF2 (2). BRG-1 is crucial to the function of the SWI/SNF nucleosome remodeling complex and interacts with various cellular factors, such as BRCA1, pRb, and several transcription factors (3–8). BRG-1 also binds to cyclin E and alters the ability of this protein to induce growth arrest (9). In SW13 cells that do not express either BRG-1 or hBrm but contain wild-type pRb, overexpression of BRG-1 leads to flat cell formation (5). A recent study by de la Serna et al. (10) demonstrated that the dominant negative form of BRG-1 blocks MyoD-mediated muscle differentiation. Interestingly, a BRG-1 null mouse displays an embryonic lethal phenotype and its heterozygotes are predisposed to exencephaly and tumors, indicating that this protein plays a role in the suppression of tumor formation (11). The nuclear receptor co-repressor and mSin3A co-purify with the SWI/SNF complex, suggesting that these distinct multiprotein complexes are involved in transcriptional repression (12, 13). Although the detailed molecular mechanism of interaction between SWI/SNF and the co-repressor complex remains to be elucidated, we speculate that the two complexes act in concert to repress target genes, using histone deacetylase (HDAC) and chromatin remodeling activity.

Human papillomaviruses (HPVs) of the high-risk group (e.g. HPV-16) cause cancers in humans, whereas papillomaviruses of the low-risk group (e.g. HPV-11) cause benign epithelial hyperproliferation (14). Papillomavirus E7 associates with pRb, and consequently deregulates pRb-mediated cell cycle arrest (15–17). E7 contains a LXCXE motif that specifically binds the pocket domain of pRb (18). Mutations in the LXCXE motif result in cellular transformation defects, suggesting that Rb-E7 binding is significant for deregulation of the cell cycle (19, 20). Recent studies (19–24) demonstrate that cell proliferation stimulation by HPV E7 is not related to Rb-E7 binding affinity, suggesting that Rb is not the only cellular targets of E7 required for its transformation potential. Previous reports indicate that E7 co-precipitates with HDAC activity and associates with HDAC1 and HDAC2 indirectly via Mi2-β, which belongs to the NURD complex (25). Moreover, Mi2-β, an SNF2 homolog, binds the COOH terminus of E7. Mutations at the E7 COOH terminus impair the ability to block the flat cells. These results imply that the COOH terminus of E7 is required to deregulate cell cycle arrest by pRb. Although details of the molecular link between the HDAC complex and E7 are unknown, we speculate that E7 may interfere with the HDAC activity by sequestering the complex away from its target genes or disrupting proper complex formation.

In this study, we show that human papillomavirus type 16 (HPV-16) E7 functionally binds BRG-1 and that mutations at the E7 COOH terminus impair its ability to prevent cell cycle arrest mediated by BRG-1 overexpression. In addition, BRG-1 contains a trichostatin A (TSA)-sensitive repression domain, and E7 perturbs the repression function of this protein. These
data suggest that the viral oncoprotein E7 bypasses cell cycle arrest by direct, but distinct interactions with pRB and BRG-1.

**EXPERIMENTAL PROCEDURES**

*Plasmid Constructs*—pBJ5-BRG-1 and pBJ5-BRG-1(K798R) were generously provided by Dr. Jerry Crabtree. The pGL3-c-fos plasmid was a gift from Dr. Akiko Tabuchi. pFLAGCMV2-2B was a gift from Dr. J. Rho. E6 or E7 open reading frames from various HPV were amplified by polymerase chain reaction using appropriate sets of primers and cloned into pGEX4T-1, pME18S, pEBG, pCGN2HA, and pEGFP-C1 vectors. HPV-16 E7 mutant open reading frames were provided by Dr. S. Um, whereas HDAC1, SMRT, and mSin3A were from Dr. Stuart L. Schreiber and Dr. Ronald M. Evans, respectively. Various deletion mutants of BRG-1 were engineered by polymerase chain reaction and cloned into the EcoRI-XhoI site of pCDNA3 and EcoRI-XhoI site of pCMV4. The pCMV4 plasmid was generated by subcloning the Swi/SnfI fragment of pM into pCDNA3. pCMV4-16E7 and pCMV4-BRG-1 deletion mutants were subcloned into the EcoRI-XhoI site of pCDNA3.

*Cells, Transfections, and Reporter Assays*—293T and C33A cells were maintained in Dulbecco’s modified Eagle’s medium supplemented with 10% fetal bovine serum. SW13 cells were maintained in RPMI supplemented with 10% fetal bovine serum. At 24 h before transfection, 3 × 10⁴ 293T or C33A cells were plated in 6-cm dishes. Transfections were performed using the calcium phosphate precipitation method (26). For SW13 cells, we employed Effectene™ purchased from Qiagen. DNA was prepared using the manufacturer’s protocol (Qiagen), and total amounts of transfected DNA were adjusted by the addition of blank plasmid DNA. In some experiments, pCDNA-hisLacZ was co-transfected for normalization of transfection efficiency. Equal amounts (5 × 10⁵) of cell lysates were used for the detection of luciferase activity (Promega). Galactosidase activity was measured with the Luminescent β-galactosidase detection kit II (Clontech).

*Glutathione S-Transferase (GST) Pull-down Assays*—Wild-type GST and GST fusion proteins were expressed in Escherichia coli, bound to glutathione-Sepharose 4B beads (Amersham Biosciences), and incubated with labeled proteins expressed by *in vitro* translation using the TnT-coupled transcription-translation system, as described by the manufacturer (Promega). Radiolabeled, *in vitro* translated proteins were incubated with GST fusion protein in T buffer (50 mM Tris-HCl, pH 7.5, 200 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 (Nunator) for 1 h at room temperature. The beads were washed four times with T buffer or EBC buffer, 5× loading dye (60 mM Tris-HCl, pH 6.8, 25% glycerol, 2% SDS, 14.4 mM mercaptoethanol, 0.5% bromophenol blue) was added, and the proteins were subjected to SDS-PAGE.

*Immunoprecipitation*—Cells expressing GST and GST-16E7 with HA-BRG-1 or BRG-1 were lysed in EBC buffer (27) and incubated with 25 µl of a 1:1 suspension of glutathione-Sepharose in EBC buffer for 4 h at 4°C with rocking. Glutathione-bound complexes were washed three times with EBC buffer and boiled at 95°C for 5 min in SDS sample buffer. Immunoblot analyses were performed using anti-HA monoclonal antibody (12CA5, Roche Molecular Biochemicals) or anti-BRG-1 rabbit polyclonal or anti-GST monoclonal antibody.

*Flatt Cell Formation and Senescence Assays*—The flat cell assay was performed essentially as described in Hinds et al. (28). SW13 cells in a culture dish were transfected with expression plasmids and 500 ng of pCDNA3 (encoding neomycin resistance). At 48 h post-transfection, cells were subjected to neomycin selection (400 µg/ml) for up to 10 days. Cells were washed in phosphate-buffered saline, fixed for 3–5 min (room temperature) in 2% formaldehyde, 0.2% glutaraldehyde, re-washed, and incubated at 37°C with fresh senescence-associated β-galactosidase staining solution. The experiment was performed according to the procedure of Dimri et al. (29). Senescence-associated β-galactosidase positive cells were identified as flat cells using a light microscope (×40 magnification).

**RESULTS**

**HPV E7 Deregulates Repression of the c-fos Promoter Mediated by BRG-1**—Morosov et al. (30) previously reported that HPV-16 E6 and E7 activate the c-fos promoter, and that the cAMP-responsive element site at −60 is responsible for stimulation of transcription by HPV E6 and the high-risk group, HPV E7. In addition, Murphy et al. (31) demonstrated that repression of the c-fos gene by BRG-1 is dependent on the cAMP-responsive element. Based on these earlier observations, we speculated that E7 overcomes repression of the c-fos promoter mediated by BRG-1, because E6, E7, and BRG-1 target the same cis-element of the promoter. To confirm this hypothesis, we performed transient transfection assays using a combination of expression vectors encoding BRG-1, E6, E7, and c-fos promoter in C33A cells. Because C33A cells are deficient in Rb, co-transfection of BRG-1 repressed the c-fos promoter activity slightly. Upon co-transfection of HPV-16 E7 and BRG-1, we observed that HPV-16 E7 deregulated BRG-1-mediated repression of the c-fos promoter (Fig. 1A). Surprisingly, HPV-16 E6 did not overcome the BRG-1-driven repression of the c-fos promoter, indicating that the effect of oncogenic E7 is specific. Transient transfection assays in 293T cells were performed to determine whether the above results are cell type-specific. Similar results were obtained, as shown in Fig. 1B. Stronger repression of the c-fos promoter was observed with BRG-1 in 293T cells, compared with that in C33A cells. On co-transfection with BRG-1, E7 activated the c-fos promoter in a dose-dependent manner.

**HPV-16 E7 Binds BRG-1 in Vivo**—To determine whether E7 interacts physically with BRG-1, we performed co-immunoprecipitation assays in 293T cells. The pEBG and pEBG-16E7 plasmids were transfected using the calcium precipitation method.
method (26). Twenty-four hours after transfection, GST fusion proteins were precipitated using glutathione-Sepharose 4B beads, and washed four times in EBC buffer. As shown in Fig. 2A (left panel), BRG-1 specifically co-precipitated with E7. Co-immunoprecipitation assays with a BRG-1-specific antibody additionally revealed specific co-precipitation of BRG-1 with E7 (Fig. 2A, right panel). We next performed a co-immunoprecipitation assay using HA-tagged BRG-1 and GST fused to HPV-16 E7. As shown in Fig. 2B, HA-BRG-1 specifically co-precipitated with GST-16E7, but not with GST alone. Our data indicate that HPV-16 E7 binds BRG-1 in vivo.

**HPV E7 from the High Risk Group Binds BRG-1 in Vitro**—Several lines of evidence suggest that HPV-6 E7 and HPV-11 E7, which associate weakly with Rb, show much lower efficiencies in transformation assay (17, 32). GST pull-down assays were performed, using recombinant GST E7 protein and in vitro-translated BRG-1 (Fig. 2C). Association of in vitro-translated BRG-1 with HPV E7 from the high-risk group (HPV-16 and HPV-18) was observed, but not with HPV E7 from the low-risk group (HPV-6b and HPV-11). GST pull-down data suggest that the interaction between E7 and BRG-1 is implicated in tumorigenesis by the HPV oncoprotein E7 (16).

**HPV E7 Binds Conserved Regions II and III of BRG-1 in Vitro**—To identify the BRG-1 region interacting with E7, we constructed deletion mutants of BRG-1 and performed in vitro binding assays. As shown in Fig. 3A, BRG-1 was divided into four conserved regions and fragments were cloned downstream of the T7 promoter for in vitro translation. Luciferase was used as a negative control. GST pull-down assays revealed that E7 specifically bound conserved regions II (amino acids 350–571) and III (amino acids 729–1041). The conserved region II is the SSX-SYT oncoprotein-binding domain, whereas region III is the ATPase domain of BRG-1. These results indicate that high-risk group E7 may play a similar role to SYT-SSX by deregulating BRG-1 function (33).

**The Intact COOH Terminus of E7 Is Required for Binding to BRG-1**—To establish whether transformation-defective E7 mutants interact with BRG-1, we constructed recombinant GST fusion proteins of E7 (Fig. 4A). A collection of plasmids encoding mutated E7 proteins was generously provided by Dr. Soo-Jong Um, Sejong University, Seoul. E7 A-(21–24) is a Rb-binding defective mutant, whereas E7 C58G/C91G represents a zinc finger-disrupted mutant, and S71I is a control mutant with similar transformation potential as wild-type E7. As shown in Fig. 4A, all mutants except C58G/C91G bound to BRG-1. To verify whether the COOH terminus of E7 is required for protein-protein interaction between BRG-1 and 16E7, we performed the in vivo binding assay using wild-type E7 and mutants E7 in 293T cells. As expected, E7 C58G/C91G did not bind BRG-1.
Interaction between HPV-16 E7 and BRG-1

Fig. 4. Zinc finger motifs of E7 are required for functional interactions with BRG-1. A, top, diagram of the HPV-16 E7 protein. The location of mutations used in this study is indicated as an arrow. Bottom, recombinant GST fusion proteins of E7 were purified using GST resin.GST pull-down assays were performed with in vitro translated BRG-1. After extensive washing, bound proteins were analyzed by SDS-PAGE and autoradiography. Input, in vitro translated BRG-1 protein. B, immunoprecipitation of BRG-1 and Rb with the E7 or E7 mutants. Left, pBJ5-BRG-1 and pCGN2HA-16E7 or mutants 16E7 were co-transfected into 293T cells. After 24 h later, we performed immunoprecipitation assay using HA monoclonal antibody. Right, pFLAGCMV2-Rb and pCGN2HA-16E7 or mutants 16E7 were co-transfected into 293T cells. C, BRG-1 binding-defective mutant E7 does not deregulate BRG-1-mediated repression of the c-fos promoter. We employed 0.25 μg of c-fos-Luc and 3 μg of E7 expression vectors in each indicated transfection. The β-galactosidase expression vector was included in each transfectant, and corresponding β-galactosidase activities were assayed.

bind to BRG-1 in vivo, confirming that the COOH terminus of E7 is important for interactions with this protein (Fig. 4B, left panel). As a control, we performed immunoprecipitation using HA-tagged E7 and FLAG-tagged Rb in 293T cells. As shown in Fig. 4B (right panel), Rb did not bind to E7 Δ-(21–24), whereas Rb associated with wild-type E7 and E7 C58G/C91G. It is known that the E7 C58G/C91G mutant is unable to bypass growth arrest signal, transform normal cells, or associate with Mi2-β (25). These results support the theory that E7 C58G/C91G does not inhibit repression of the c-fos promoter mediated by BRG-1. To verify this hypothesis, we co-transfected wild-type E7 and its mutants into 293T cells. As shown in Fig. 4B, only the zinc finger mutant did not affect repression of the c-fos promoter mediated by BRG-1. Our data therefore suggest that the association between BRG-1 and E7 is important for E7-mediated transformation.

The COOH Terminus of HPV-16 E7 Is Required for Blocking Flat Cell Formation by BRG-1—Previous studies showed that BRG-1 mediates flat cell formation in SW13 cells (24). Moreover, co-transfection of HPV-16 E7 and Rb into Saos-2 cells deficient in Rb and p53 results in flat cell formation (25). If Rb-BRG-1 is important for flat cell formation and E7 blocks both proteins, the Rb binding-deficient E7 mutant should block this process in conditions where BRG-1 is overexpressed in SW13 cells. Because SW13 cells are deficient in BRG-1 and Brm and contain intact Rb, they were employed as a model cell line in this study. As expected, stable transfection of BRG-1 into SW13 cell lines resulted in flat cell formation and senescence phenotype (Fig. 5A). Transfection of BRG-1 plus HPV-16 E7 rescued SW13 cells from flat cell formation, whereas the zinc finger mutant of HPV-16 E7 did not affect this process, indicating that only oncogenic E7 blocks BRG-1-mediated formation of flat cells. The results of the flat cell formation assay using wild-type E7 and various mutants are summarized in Fig. 5B. The Rb binding-defective mutant (Δ-(21–24)) did not differ significantly from wild-type E7 in overcoming the ability of BRG-1 to produce flat cells. These results indicate that deregulation of Rb by E7 is not related to the blockage of BRG-1-mediated flat cell formation. In contrast, the S71I mutant, which retains BRG-1 binding, deacetylase binding, and Rb binding activity, showed a similar phenotype of wild-type E7 (23, 25) (Fig. 4A). We also examined the phenotype of another COOH-terminal mutant (L67R). Both mutant proteins displayed similar phenotypes on co-transfection with BRG-1 (data not shown). From these data, we conclude that oncogenic E7 blocks BRG-1-mediated flat cell formation, distinct from its Rb binding activity.

HDAC Components and BRG-1 Synergistically Repress the c-fos Promoter, Which Is Affected by E7—To determine whether BRG-1-mediated repression of the c-fos promoter is deregulated by TSA, BRG-1 and the c-fos promoter were co-transfected into 293T cells in the presence or absence of 2 nM TSA. As shown in Fig. 6A, transcriptional activity of the c-fos promoter was repressed by BRG-1 in the absence of TSA. In contrast, no repression of c-fos promoter activity was observed in the presence of TSA. Next, we examined whether repression of c-fos promoter by BRG-1 was influenced by HDAC components, such as SMRT, HDAC1, and mSin3A. As shown in Fig. 6B, the presence of HDAC components led to more effective repression of the c-fos promoter. Finally, another reporter assay was performed under similar experimental conditions, whereby HPV-16 E7 was employed to examine whether E7 blocks the repressive effects of BRG-1 and HDAC components. As shown in Fig. 6C, E7 deregulated BRG-1 and HDAC-mediated repression of the c-fos promoter. We therefore conclude that E7 mitigates the repressive forces of BRG-1 and HDAC components on the c-fos promoter in vivo.

BRG-1 Contains a TSA-sensitive Repression Domain and E7 Inhibits the Transcriptional Repression Ability of BRG-1—
Mechanisms of transcriptional repression are categorized into either passive or active repressor (34). Passive repressors function by the competitive inhibition of activators, whereas active repressors per se repress transcription by interacting with general transcription factors or recruiting co-repressor complexes. Accordingly, we investigated whether BRG-1 acts as an active or passive repressor. For this purpose, full-length BRG-1 and derivatives were fused to the Gal4 DNA-binding domain. Using a Gal4-dependent reporter (Gal4-ML-Luc), we artificially recruited BRG-1 into the promoter region. As shown in Fig. 7A, Gal4-BRG-1-(1-1336) displayed repressive activities, whereas Gal4-BRG-1-(1-336) exhibited stimulatory activity. Gal4 alone and Gal4-BRG-1-(350-571) did not display transcriptional activity. On the addition of TSA (2 nM) under the same experimental conditions, transcriptional repression activity of Gal4-BRG-1, Gal4-BRG-1-(1-1336) and Gal4-BRG-1-(729-1041) was abolished. These results indicate that BRG-1 contains a TSA-sensitive repressive domain, characteristic of an active repressor.

We additionally tested whether the repressive activity of BRG-1 was enhanced further by HDAC1. As expected, Gal4-BRG-1-(1-729) exhibited stimulatory activity. Gal4 alone and Gal4-BRG-1-(1-1041) displayed repressive activities, whereas Gal4-BRG-1-(1-2124) was abolished.

The c-fos promoter. A, E7 blocks repression of the c-fos promoter by BRG-1 and HDAC components. BRG-1-mediated repression of the c-fos promoter is sensitive to TSA. The amount of transfected pBj5-BRG-1 is indicated below each bar. The final TSA concentration employed was 2 nM. B, HDAC components and BRG-1 synergistically repress the c-fos promoter. 293T cells were co-transfected with a combination of 0.1 μg of c-fos, 1 μg of BRG-1, and 0.5 or 1 μg of HDAC component expression vectors. C, E7 inhibits repression of the c-fos promoter by BRG-1 and HDAC components.

**DISCUSSION**

A large amount of evidence has suggested that E7 is important for the development of cervical cancer by deregulating pRb (15–17). Although the precise mechanism by which E7 bypasses growth arrest signal is not elucidated, mutants of E7 that fail to bind to pRb do not override the growth suppression signal (35). These data indicate that the inactivation of Rb and consequent activation of E2F transcription factors are required for progression into S phase. The importance of the COOH-terminal domain of E7 has been documented by several groups (19, 24, 35, 36). Recently, it was reported that Rb binding to E7 is not sufficient to transform normal cells (37). In fact, zinc finger mutants of E7 do not transform human keratinocyte cells (24). These results implicate that other cellular targets of E7 are necessary for its oncogenic potential. We observed that a zinc finger mutant of E7 C58G/C91G did not bind BRG-1 and failed to overcome cell cycle arrest in SW13 cells, indicating that the physical association between viral oncogene E7 and BRG-1 is important for the control of cellular proliferation. Another zinc finger mutant (L67R) of E7 also displayed defects in progression into S phase (35). These data indicate that the inactivation of Rb and consequent activation of E2F transcription factors are required for progression into S phase. The importance of the COOH-terminal domain of E7 has been documented by several groups (19, 24, 35, 36). Recently, it was reported that Rb binding to E7 is not sufficient to transform normal cells (37). In fact, zinc finger mutants of E7 do not transform human keratinocyte cells (24). These results implicate that other cellular targets of E7 are necessary for its oncogenic potential. We observed that a zinc finger mutant of E7 C58G/C91G did not bind BRG-1 and failed to overcome cell cycle arrest in SW13 cells, indicating that the physical association between viral oncogene E7 and BRG-1 is important for the control of cellular proliferation. Another zinc finger mutant (L67R) of E7 also displayed defects in BRG-1 binding and did not block flat cell formation in SW13 cells (data not shown). These results correlate the interactions between BRG-1 and E7 with the transformation potential of E7.

Activation of transcription by specific factors requires a chro-
Fig. 7. Repression by BRG-1 in a GAL4 fusion protein assay. A, right panel, BRG-1 displays the characteristics of an active repressor. Expression vectors (2 μg) encoding full-length BRG-1, different structural domains of BRG-1 fused to the GAL4 DNA-binding domain, or a GAL4 DNA-binding domain only as a control were co-transfected into 293T cells. Whole cell extracts at 24 h after transfection were subjected to Western blotting with a monoclonal antibody (Santa Cruz, sc-510) against GAL4 DNA-binding domain. All proteins were expressed properly. Although our hypothesis requires confirmation using a more detailed in vitro transcription system, viral proteins such as E7 are currently useful models for these analyses.

Our preliminary data indicate that E7 increases the acetylation status of the c-fos promoter region in vivo by alleviating the BRG-1-HDAC complex from the promoter region (data not shown). However, we cannot rule out the possibility that the ectopic expression of E7 increases bulk histone acetylation and histone acetylation itself is not important for E7-mediated transcriptional activation of c-fos promoter. Previous studies indicate that histone acetylation is not sufficient for chromatin remodeling and gene expression in vivo (44, 45). In this view, the additional targeting of co-activator or transcription factors by E7 may be the critical events in transcriptional activation of c-fos promoter.

Our studies provide novel evidence that the COOH terminus of the viral oncogene E7 interacts with a candidate tumor
suppressor, BRG-1. It would be of interest to determine whether E7 blocks BRG-1-mediated chromatin remodeling as well as chromatin modification.

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