Human Papilloma Virus 16 E6 Oncoprotein Inhibits Retinoic X Receptor-mediated Transactivation by Targeting Human ADA3 Coactivator

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The expression of human papillomavirus (HPV) E6 oncprotein is causally linked to high-risk HPV-associated human cancers. We have recently isolated hADA3, the human homologue of yeast transcriptional co-activator yADA3, as a novel E6 target. Human ADA3 binds to the high-risk (cancer-associated) but not the low-risk HPV E6 proteins and to immortalization-competent but not to immortalization-defective HPV16 E6 mutants, suggesting a role for the perturbation of hADA3 function in E6-mediated oncogenesis. We demonstrate here that hADA3 directly binds to the retinoic X receptor (RXR) in vitro and in vivo. Using chromatim immunoprecipitation, we show that hADA3 is part of activator complexes bound to the native RXR response elements within the promoter of the cyclin-dependent kinase inhibitor gene p21. We show that hADA3 enhances the RXRα-mediated sequence-specific transactivation of retinoic target genes, cellular retinoic acid-binding protein II and p21. Significantly, we demonstrate that E6 inhibits the RXRα-mediated transactivation of target genes, implying that perturbation of RXRα-mediated transactivation by E6 could contribute to HPV oncogenesis.

The human papillomavirus are causally linked to more than 90% of the cases of cervical cancer (1, 2). Numerous studies have defined the critical roles of two HPV1 oncogenes E6 and E7 in oncogenesis. These oncogenes are invariably expressed in HPV-associated carcinomas and cell lines derived from these cancers (3, 4). Intact E6 and E7 open reading frames are required for in vitro immortalization of human epithelial cells by the HPV genome, and E6 and/or E7 genes are sufficient to immortalize these cells (5–8).

A crucial aspect of the oncogenic mechanism of E6 and E7 involves their ability to inactivate two key cell cycle checkpoint proteins, p53 and retinoblastoma protein, respectively (9, 10). While E6-induced loss of p53 strongly correlates with E6-induced cellular transformation, recent studies have identified additional cellular targets of E6 that are likely to play important roles in HPV oncogenesis (11, 12). Defining the roles of these novel E6 targets is of substantial importance to fully understand the mechanisms of HPV-mediated oncogenesis.

Using the yeast two-hybrid interaction system, we recently identified hADA3 as a novel E6-binding protein (13). hADA3 is the human homologue of yeast transcriptional co-activator yADA3 (alteration/deficiency in activation 3). We have demonstrated that hADA3 binds to the high-risk (cancer-associated) but not to the low-risk HPV E6 proteins, and to immortalization-competent but not to immortalization-defective HPV16 E6 mutants, implying a role for E6-induced hADA3 inactivation in oncogenic transformation.

Genetic studies in yeast have demonstrated that ADA3 functions as a critical component of coactivator complexes that link transcriptional activators, bound to specific promoters, to histone acetylation, and basal transcriptional machinery (14–16). The core components of this complex include the adapter proteins ADA3 and ADA2 and a histone acetylase GCN5 (general control non-repressed 5) (17). Importantly, hADA3 exists as a component of a yeast ADA-like complex that includes hADA2 and hGCN5, indicating that the functional roles of ADA complex are evolutionarily conserved (18). Studies of mammalian retinoic X receptor (RXR) and growth hormone receptor when expressed in yeast have shown a requirement for the components of yeast ADA complex including the yADA3 gene product (19, 20). However, a functional role of hADA3 in nuclear hormone receptor transactivation in mammalian cells has not yet been defined.

Given the important role of the inactivation of p53 transactivation in E6-induced oncogenesis, our earlier studies focused on the novel role of hADA3 as a p53 coactivator (13). Another group has also reported a coactivator function of hADA3 for p53 (21). Our studies also established that the interaction of hADA3 with E6 led to its ubiquitin-mediated degradation (13). In view of the strong yeast genetic data for a potential role of hADA3 as a coactivator for nuclear hormone receptors, our isolation of hADA3 as an E6-binding protein raised the possibility that E6 may inactivate the mammalian nuclear hormone receptor function by targeting hADA3. In this study, we exami-
**HPV E6 Inhibition of RXR Transactivation Via hADA3**

**EXPERIMENTAL PROCEDURES**

**Plasmid Constructs—Generation of the expression constructs of full-length hADA3 and FLAG-hADA3 in the pCR3.1 vector (Invitrogen) has been described previously** (13). The pGEX-4T-1-hADA3 construct encoding the GST-hADA3 fusion protein and pCR3.1-encoding the HPV16 E6-MYC construct, encoding the Myc-tagged HPV16 E6, were kindly provided by Dr. M. Ishibashi (Aichi Cancer Center, Japan). The pSG5-RXR and pSG5-RAR expression constructs were used as templates to generate the GST-hADA3 fusion protein and pCR3.1-encoding the HPV16 E6-MYC construct, encoding the Myc-tagged HPV16 E6, after cloning into pGEX-4T-1 and pCR3.1.

*In Vitro Binding between hADA3 and Retinoid Receptors*—The pSG5-RXX and pSG5-RAR expression constructs were used as templates in a rabbit reticulocyte lysate-based (TNT rabbit reticulocyte lysate system; Promega, WI) or an *E. coli* expression system (22). These findings prompted us to examine if hADA3 functions as a coactivator for retinoid receptor proteins in human cells and whether E6 interaction with hADA3 would allow it to perturb the retinoid receptor function.

**RESULTS AND DISCUSSION**

There is an emerging consensus that cellular transformation by viral oncoproteins disrupts multiple cellular pathways that control cell proliferation, differentiation, migration, and other critical cellular traits. Identification and characterization of cellular targets of human cancer-associated viral oncoproteins is therefore of great interest in cancer research as well as in basic cellular biology. We previously identified human ADA3, homologue of the yeast ADA3 transcriptional coactivator, as a critical cellular trait. Identification and characterization of cellular targets of human cancer-associated viral oncoproteins is therefore of great interest in cancer research as well as in basic cellular biology. We previously identified human ADA3, homologue of the yeast ADA3 transcriptional coactivator, as a critical cellular trait. Identification and characterization of cellular targets of human cancer-associated viral oncoproteins is therefore of great interest in cancer research as well as in basic cellular biology.
Next, we examined if hADA3 can also interact with the RARα protein as such or in the presence of RXRα. As RXRα and RARα proteins are of a similar size to be able to unambiguously visualize RARα and RXRα proteins in the same gel, we used the ligand-binding domain of RXRα in these experiments. As shown in Fig. 1B, RXRα did not show a detectable level of direct interaction with hADA3 (Fig. 1B, lane 4, upper panel). However, when the ligand-binding domain of RXRα was included in the binding reaction, both RARα and RXRα could be pulled down with GST-hADA3 (Fig. 1B, lane 5, upper panel). Similar binding was observed when full-length RXRα was used (data not shown). Coomassie Blue staining of gels confirmed the presence of respective GST fusion proteins in the binding reactions (Fig. 1, A and B, lower panels). These results indicate that while RARα does not directly interact with hADA3, it can do so when present as a RXRα/RARα heterodimer.

**RARαs and RARαs Associate with hADA3 Protein in Vivo**—In view of the *in vitro* binding, we used co-immunoprecipitation analyses of transfected proteins to assess whether hADA3 interacts with RARα and RXRα in Saos-2 cells. Anti-RXR immunoprecipitates from transfected cell lysates were subjected to anti-FLAG immunoblotting to detect co-immunoprecipitated FLAG-tagged hADA3. No hADA3 was detected in anti-RXR immunoprecipitates if cells had been transfected only with hADA3 or RARα constructs or when hADA3 plus RXRα-transfected cells had not been treated with 9-cis-RA (Fig. 2A, lanes 1–3, right panel). In contrast, hADA3 was readily detectable in anti-RXR immunoprecipitates from hADA3 plus RXRα-transfected cells treated with 9-cis-RA (Fig. 2A, right panel, lane 6). Anti-RXR immunoblotting of anti-RXR immunoprecipitates demonstrated the immunoprecipitation of RXRα in the appropriate lanes (Fig. 2A, right lower panel), and anti-FLAG and anti-RXR blotting of whole cell lysates confirmed the expected expression of hADA3 and RXRα (Fig. 2A, left panels).

Given the indirect, RXRα-mediated binding of RARα to hADA3 *in vitro*, we also examined if RARα can associate with hADA3 in the presence of RXRα, the strategy used similar to that used for RXRα, except that immunoprecipitates were carried out using an anti-RARα antibody. A substantial association between RARα and hADA3 was observed if RXRα was co-expressed, and cells were treated with 9-cis-RA (Fig. 2B, lane 8, right upper panel). Immunoblotting of anti-RARα immunoprecipitates (right lower panel) showed the RARα protein in the appropriate lanes, and the expected expression of hADA3 or RARα was confirmed by immunoblotting of whole cell lysates (left panels). The above results were confirmed in 293T cells (data not shown). Taken together, our results demonstrate a direct interaction of hADA3 with RXRα, which allows it to associate with RXRα homodimers as well as RXRα/RARα heterodimers.

**ADA3 Is Present in Activator Complexes Bound to RARE of the Native p21 Promoter**—A crucial aspect of coactivator function involves their ability to assemble into complexes with transcriptional activators bound to specific promoters (27). To directly assess if hADA3 is assembled into transcriptional activator complexes bound to a native retinoid response element, we used the ChIP analysis of the retinoid-responsive p21 promoter. As p21 is p53-responsive (28) and hADA3 can function as a p53 coactivator (13, 21), we utilized 76R-30 cells, which lack p53 and fail to show a DNA damage-induced increase in the transcription of p21, unlike their normal parental cells (23). Initial experiments established that 9-cis-RA treatment of these cells led to an increase in p21 mRNA when cells were grown in regular DFCL-1 medium, without a need for retinoid deprivation (data not shown). A detectable level of p21 mRNA is seen in 76R-30 cells in the absence of stimulation (Fig. 3A, lane 1); however, 9-cis-RA treatment led to a dose-dependent increase in p21 mRNA (lanes 2–4), consistent with the presence of endogenous RXRα and RARα mRNA and protein in these cells (data not shown).

For ChIP analysis, 76R-30 cells were either mock-treated or treated with 100 nm 9-cis-RA for 24 h and then fixed with formaldehyde to cross-link the native chromatin-associated protein complexes with the DNA. The chromatin immunoprecipitation were carried out with preimmune (negative control) or anti-ADA3 antibodies (and anti-RARα and RXRα antibodies as positive controls), and the co-immunoprecipitated DNA was used as a template for the PCR to amplify the p21 promoter.
sequences that incorporate RARE (28). As shown in Fig. 3B, a clear PCR amplification product was observed in chromatin immunoprecipitation carried out with anti-ADA3 antibodies but not the preimmune serum (compare lane 7 with lane 9); the intensity of this band was significantly higher in the chromatin immunoprecipitation of 9-cis-RA-treated cells (lane 8), indicating that ADA3 was in association with the native p21 promoter and that this association was enhanced in the presence of the RXRα ligand. As expected, PCR products were amplified in chromatin immunoprecipitation carried out with anti-RXR and anti-RARα antibodies; however, no further increase was seen upon ligand treatment of cells (lanes 3–6). These results are consistent with a ligand-independent binding of RXR and RXR/ RAR to the p21 promoter, as observed with other retinoid responsive promoters by gel retardation assay (29). Amplification of promoter sequences of glyceraldehyde-3-phosphate dehydrogenase, which is not a target of retinoids demonstrated the specificity of our results. Overall, these results demonstrate that ADA3 becomes part of the activator complexes bound to a retinoid response element in its native chromatin configuration upon RXRα ligand stimulation.

hADA3 Enhances the RXRα-mediated and RXRα/RARα-mediated Transactivation of Reporters Linked to Retinoid Response Elements—Given the ability of hADA3 to interact with RXRα and with RXRα/RARα heterodimers and the previously defined role of ADA3 as a component of the ADA coactivator complex (17), we examined if hADA3 functions as a coactivator of transcription mediated by the RXRα homodimer or the RXRα/RARα heterodimer. To assess the coactivator function of hADA3 for RXRα, we transiently transfected Saos2 cells with a luciferase reporter linked to the retinoid response element derived from the CRBPII promoter; CRBPII is known to be transactivated by RXRα but not by RARα (30). Little CRBP-II-luciferase activity was detected in mock-treated cells (Fig. 4A, lane 1). In contrast, 9-cis-RA treatment of cells transfected with RXRα resulted in about a 100-fold induction of the luciferase activity (lane 2). Importantly, co-transfection of hADA3 with RXRα led to a substantial, hADA3 dose-dependent increase in ligand-induced luciferase reporter activity (lanes 4, 6, and 8). The reporter activity was not induced if hADA3 was transfected without RXRα (data not shown). Western blot of cell lysates showed the expected expression of hADA3 and RXRα proteins (Fig. 4B). These results provided evidence that hADA3 can function as a coactivator for RXRα-mediated transcription in mammalian cells.

Next, we examined the transactivation of a retinoid-responsive promoter that could be transactivated by RXRα/RARα heterodimers. For this purpose, we employed a luciferase reporter incorporating two copies of the retinoid response element from the p21 promoter (28). When the p21-luciferase reporter was transfected in Saos2 (Fig. 4, C and D) or 76R-30 (Fig. 4, E and F) cells together with RXRα and RARα, a substantial ligand-inducible increase (about 30-fold in Saos2 cells (Fig. 4C, compare lane 1 with lane 2) and 100-fold in 76R-30 cells (Fig. 4E, compare lane 1 with lane 2) in luciferase activity was observed. Importantly, cotransfection of ADA3 together with RXRα and RARα resulted in a dramatic, ADA3 dose-dependent, increase in 9-cis-RA-induced luciferase activity in both Saos2 (Fig. 4C, lanes 4, 6, and 8) and 76R-30 cells (Fig. 4E, lanes 4, 6, and 8). Immunoblotting of cell lysates showed the
expected expression of transfected proteins (Fig. 4, D and F). Interestingly, although the levels of ADA3 in 76R-30 cells were much lower than Saos2 cells (probably due to lower transfection efficiency of 76R-30 cells as compared with Saos2), the coactivator function of ADA3 is comparable in both cells (Fig. 4, compare C and D with E and F). Although the reason for this difference is currently unknown, it could reflect differences of cellular origin (epithelial versus fibroblasts). Taken together, these results demonstrated that hADA3 can function as a coactivator for RXRα as well as the RXRα/RARα heterodimer in mammalian cells.

**HPV16 E6 Inhibits the Coactivator Function of hADA3**—Given the ability of HPV16 E6 to interact with and induce the degradation of hADA3 (13), we examined the effect of coexpressing E6 on hADA3-induced increase in RXRα-mediated transactivation of CRBPII-RARE-Luc reporter. For this purpose, Saos2 cells were transfected with RXRα and hADA3 together with either wild-type E6 or a hADA3 non-binding E6 mutant Δ9–13. While hADA3 expectedly enhanced the 9-cis-RA-induced, CRBPII luciferase reporter activity in RXRα-transfected cells (Fig. 5A, compare lane 2 with lane 4), neither E6 nor its mutant by itself had any effect on the RXRα-dependent reporter activity (Fig. 5A, lanes 11–16). Significantly, cotransfection of wild-type E6 dose-dependently inhibited the hADA3-induced increase in RXRα-mediated CRBPII luciferase reporter activity (Fig. 5A, lanes 6 and 8); in contrast, the hADA3 non-binding Δ9–13 E6 mutant had no effect (Fig. 5A, lane 10). As anticipated (Kumar et al., Ref. 13), the expression of wild-type E6 but not its ADA3 non-binding mutant was accompanied by a reduction in hADA3 levels (Fig. 5B, compare lanes 2–5). Immunoblotting of cell lysates confirmed the expected expression of hADA3 and RXR proteins (Fig. 5B, lower panel, shown only for 9-cis-RA-treated cell lysates).

To further confirm the ability of E6 to inhibit the coactivator function of ADA3 for retinoid receptor-mediated transactivation, we utilized the p21 promoter-luciferase reporter; the cells were co-transfected with RXRα and RARα. As with CRBPII reporter, the p21 luciferase reporter activity was dose-dependently inhibited by the expression of wild-type E6 but not its Δ9–13 mutant (Fig. 5C, lanes 6, 8, and 10). Immunoblotting of cell lysates confirmed the expression of hADA3, RXRα, and RARα (Fig. 5D). Taken together, our results clearly demonstrate that HPV16 E6 abrogates the coactivator function of hADA3 toward retinoid receptors RXRα and RARα in human cells.

The results presented here have significant implications for the potential role of ADA3-containing coactivator complexes in physiological pathways and in oncogenesis. While yeast ADA3 as a component of ADA and other coactivator complexes has been clearly demonstrated to be important, little was known about hADA3 function in mammalian systems except for its ability to function as a p53 coactivator, which others and we have recently uncovered (13, 21). Our results that hADA3 functions as a coactivator for retinoid receptors in mammalian cells, together with the ability of yeast ADA3 to function as a coactivator of multiple mammalian nuclear hormone receptors when these were expressed in yeast, strongly suggest that ADA3-containing complexes may participate as coactivators for multiple nuclear hormone receptors. While a recent study failed to detect mouse ADA3 association with estrogen receptor (31), yeast ADA3 has been shown to coactivate estrogen receptor (ER) function, and we have detected a direct interaction between hADA3 and ER. The presence of HGCN5 as well as a HGCN5-related gene product P/CAF in hADA3-containing complexes (18), direct interaction of P/CAF with p300/CBP (32), and the interaction of hADA3 itself with p300 (21) suggest that hADA3 may form multiple, distinct coactivator complexes, as also is the case in yeast (17). Thus, it is likely that additional transcriptional activators will emerge as targets of ADA3 coactivator function.

Our findings that HPV16 E6 abrogates the coactivator function of hADA3 have obvious implications for the potential role of the hADA3-mediated biochemical pathways in oncogenesis. The role of presently known ADA3 targets (p53 and retinoid receptors) in cell growth and differentiation is well established, and these pathways are frequently affected during oncogenesis. Thus, if E6 indeed targets the various hADA3-containing complexes and influences transcriptional pathways in which these complexes play a role, this could represent a significant mechanism for the role of E6 in HPV-mediated oncogenesis.

Our findings support the emerging concept that viral onco-
hADA3 enhances the RXRα-mediated transactivation of reporters linked to RARE. A. Saos2 cells were deprived of retinoids by growth in charcoal-treated phenol-free α-MEM medium for 48 h, transfected with 100 ng of CRBPII-RARE-Luc and 40 ng of RXRα plasmids together with increasing amounts of pCR3.1-hADA3, using the FuGENE 6 reagent. The total amount of DNA for each transfection was kept constant by adding vector DNA. After 24 h, the cells were either mock-treated (−) or treated with 100 ng 9-cis-RA (+) for 24 h prior to lysis. 20 ng of SV40 Renilla luciferase reporter (pRL-SV40) was concurrently transfected and used to correct for differences in transfection. Equal amounts of cell lysates were used to measure the luciferase activity. Transactivation results were calculated as fold activation over vector-transfected cell lysates. Data indicates mean ± S.D. of triplicates of a representative experiment. Experiments were repeated at least three times. −, vector DNA.
proteins, such as HPV E6, have attained an ability to perturb the function of multiple transcriptional coactivators apparently by multiple mechanisms. Notably, E6 oncoprotein has been demonstrated to associate with p300, which serves as a coactivator for a number of transcription factors, including nuclear hormone receptors (33, 34). While the effect of HPV E6 binding to p300 on nuclear receptor-mediated transcription has not been examined, E6 is known to abrogate the coactivator function for p300 toward p53 (33, 34). Recently, another E6-binding protein AMPF1 (also called G-protein pathway suppressor 2 or GPS2), was shown to be a coactivator for p53 (35, 36). These studies are consistent with the idea that E6 has attained an ability to perturb multiple coactivators. How might the E6 perturbation of coactivator function promote oncogenic transformation? We envision that E6 interaction with hADA3 would disrupt the hADA3-containing HAT complexes, prevent the recruitment of HAT activity to promoter elements, and inhibit the expression of genes that mediate tumor suppressor functions. The role of histone acetylation as a tumor suppressor mechanism is supported by the propensity of CBP + heterozygous mice to develop hematopoietic malignancies (37), and the ability of RARα fusion oncogenes, which recruits histone deacetylases to RAREs (38), to induce promyelocytic leukemia by inhibiting cell differentiation. Indeed, histone deacetylase inhibitors together with retinoid are now being assessed for treatment of such patients (38–40). Thus, it is reasonable to postulate that ADA3, as a component of HAT-containing coactivator complexes, plays a role in transcription of genes. A large body of evidence supports an important role of retinoids in cell differentiation and cell growth inhibition (41–44). There is also increasing evidence that retinoids down-regulate the telomerase in a pathway distinct from cell differentiation, implicating the role of retinoids in replicative senescence (45, 46). Complementary in vivo studies have demonstrated the ability of retinoids to inhibit tumor formation in carcinogenesis models, typically at the step of tumor promotion (47, 48). Importantly, these studies have led to clinical trials of retinoids in chemoprevention of a number of epithelial and non-epithelial cancers (49).

In conclusion, we have shown hADA3 directly interacts with...
RXRα and functions as a coactivator for RXRα and RARα/RXRα-mediated transactivation. In addition, we show that HPV16 E6 by targeting hADA3 for degradation, abrogate the RXRα-mediated transactivation, implicating disruption of retinoid receptor function in E6 oncogenesis. Given the evolutionary conservation of hADA3, it is likely that viral oncoprotein-mediated inactivation of its function plays an important role in oncogenesis.

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