Small DNA tumor viruses such as simian virus 40 (SV40) and polyomavirus (Py) take advantage of host cell proteins to transcribe and replicate their DNA. Interactions between the viral T antigens and host proteins result in cell transformation and tumor induction. Large T antigen of SV40 interacts with p53, pRb/p107/p130 family members, and the cyclic AMP-responsive element-binding protein (CREB)-binding protein (CBP)/p300. Py large T antigen is known to interact only with pRb and p300 among these proteins. Here we report that Py large T binds to CBP in vivo and in vitro. In cotransfection assays, Py large T inhibits the co-activation functions of CBP/p300 in CREB-mediated transactivation but not in NF-κB-mediated transactivation. p53 appears not to be involved in the functions of CREB-mediated transactivation and is not essential for large T:CBP interaction. Mutations introduced into a region of Py large T with homology to adenovirus E1A and SV40 large T prevent binding to the co-activators. These mutant large T antigens fail to inhibit CREB-mediated transactivation. The CBP/p300-binding Py mutants are able to transform established rat embryo fibroblasts but are restricted in their ability to induce tumors in the newborn mouse, indicating that interaction of large T with the co-activators may be essential for virus replication and spread in the intact host.

Interactions between viral proteins and a variety of host cell factors are critical for virus growth. DNA tumor viruses such as human adenovirus, simian virus 40 (SV40), human papillomavirus (HPV), and polyomavirus (Py) encode viral proteins that interact with cellular factors involved in apoptosis, cell cycle regulation, and differentiation. Tumor suppressors p53 and retinoblastoma protein (pRb) are among the best known of these. Adenovirus E1B and SV40 large T antigen complexes with p53, thereby blocking apoptosis (1, 2). The E6 oncoproteins of the “high risk” HPV such as HPV-16 and HPV-18 bind p53 and induce its rapid degradation (3). Adenovirus 12 S and 13 S E1A proteins, SV40 large T, and the E7 proteins of HPV-16 and HPV-18 form stable complexes with the family of retinoblastoma tumor suppressor gene products (pRb, p107, p130), leading to release of cells from G1 arrest (4–6). Py large T antigen also binds to pRb (7, 8) but has no apparent interaction with p53 (9, 10). Py mutants unable to bind pRb fail to induce G1 to S cell cycle progression and are defective in virus growth in cell culture (11). These mutants fail to immortalize primary cells but are able to induce tumors when inoculated into newborn mice (7).

The CBP/p300 transcriptional co-activators are also targeted by oncogenic viruses. These homologous proteins have three C/H-rich domains (12). They function as co-activator proteins for many transcription factors, including p53 (13, 14), cyclic AMP-responsive element-binding protein (CREB) (15), nuclear receptors (16), AP-1 (17), NF-κB (18, 19), NFAT (20), and STAT-1 (21). They also interact with the basal transcription factor TFIIB, which in turn is associated with the TATA box-binding protein (22). These co-activators have histone acetyltransferase activity known to be involved in transcription activation (23). Binding of viral proteins to CBP/p300 has been found in many viruses and would appear to be critical for virus growth. The human leukemia virus type 1 Tax oncoprotein, Epstein-Barr virus nuclear protein 2, and human immunodeficiency virus 1 Tat protein have all been found to interact with the CBP/p300 family (24–27). Among the small DNA tumor viruses, E1A and SV40 large T as well as E6 protein of HPV-16 bind to CBP/p300 and inhibit the transcriptional activity of CBP/p300 (28–31). Regions of CBP/p300 involved in binding to E1A have been determined (21). Two critical sequences on E1A for binding CBP/p300 have also been defined (32). A subspecies of p300 with high histone acetyltransferase activity has been shown to co-precipitate with Py large T (33). The functional consequences of this interaction and the binding regions involved remain unknown.

In this report we identify a specific site in Py large T that is critical for binding CBP/p300 and introduce mutations to help evaluate the associated functions in cell culture and in the mouse. Using reporter gene constructs and cotransfection, we show that wild type but not mutant large T inhibits CREB-mediated transactivation. Unlike the pRb-binding mutants, which are competent both to transform cells in culture and to induce tumors in the mouse, the CBP/p300-binding mutant transforms but is defective in inducing tumors, suggesting a primary block in virus replication.

**EXPERIMENTAL PROCEDURES**

**Cells and Viruses**—NIH 3T3 cells, PyF, WOP, BR-IT, and Py6 cells were routinely cultured in Dulbecco’s Modified Eagle’s medium supplemented with 0.375% sodium bicarbonate, 100 units/ml penicillin, 100 μg/ml streptomycin, and 5% calf serum in a 5% CO2 incubator at 37 °C. p53” mouse embryo fibroblasts (MEFs) were obtained from Dr. J. DeCaprio and from our laboratory (9). These were maintained in the same medium except 10% fetal bovine serum (FBS) was used in place of...
calf serum. The RB1 mutant virus expressing a large T mutant that fails to bind pRb (7) and the wild type “high tumor” polyomavirus strain PTA (34) have been described. The PTA-P671L mutant virus was grown by transfecting BR-IT cells (35) with the mutant viral DNA (see below).

Plasmids—GST-CBP fusion plasmids and CMV-p65/86/40 were provided by T. Collins. GST-p300 plasmids were provided by Dr. M. Joo. CMV-p300 and CMV-E1A plasmids and AC26 antibody were provided by D. Livingston. RSV-CBP and RSV-PK-A plasmids were provided by R. Goodman. To construct CMV-LT, rC dCDNA was amplified by polymerase chain reaction and subcloned into pcDNA3 (Invitrogen). Other plasmids used in transient transfection assays were purchased from Stratagene.

In Vitro Binding Assays—GST fusion proteins were expressed in Escherichia coli and extracted as described (36). The GST fusion proteins immobilized on glutathione-Sepharose 4B were incubated with cell extracts prepared as described below for 2 h at 4 °C in Nonidet P-40 lysis buffer (0.1 37 M NaCl, 0.02 M Tris-HCl, pH 8.0, 1 mM MgCl$_2$, 0.1 mM CaCl$_2$, 10% glycerol, 1% Nonidet P-40, 2 μM NaF, 0.1 μM Na$_3$VO$_4$, 1 mM phenylmethylsulfonyl fluoride, 20 μg/mL leupeptin, 10 μg/mL aprotinin) and washed five times with the same buffer. The bound proteins were eluted with SDS sample buffer and separated by 12% SDS-PAGE, followed by transfer to nitrocellulose membranes. The membranes were blocked with 5% nonfat dry milk in TNET buffer (10 mM Tris, 2.5 mM EDTA, 50 mM NaCl, and 0.1% Tween 20), and incubated with F4 mouse monoclonal anti-T antibody for 1 h at 4 °C. The blots were washed four times with TNET buffer (10 mM Tris, 2.5 mM EDTA, 50 mM NaCl, and 0.1% Tween 20) and then incubated with secondary antibody conjugated to horseradish peroxidase, and then washed four times in TNE buffer. The T antigen bands were visualized by chemiluminescence (PerkinElmer Life Sciences).

Co-immunoprecipitation and Immunoblotting—About 2 × 10$^6$ cells were extracted with 350 μl of Nonidet P-40 lysis buffer for 20 min at 4 °C, and lysates were cleared by centrifugation at 13,000 × g for 10 min. The supernatants were incubated with 10 μg of protein against to CBP (A-22, Santa Cruz) for 4 h at 4 °C, and the immune complexes were collected by adding 40 μl of Protein G Plus/Protein A-agarose beads (Oncogene Research Products) and incubating samples for 2 h at 4 °C, followed by six washes with Nonidet P-40 lysis buffer. After SDS-PAGE and transfer to nitrocellulose membrane, the bound T antigen was detected with F4 antibody by Western blot analysis as described above. For CBP detection on nitrocellulose membrane, the membrane was blotted with mouse monoclonal anti-CBP antibody (AC26, gift from Dr. David Livingston) and subsequently incubated with secondary antibody followed by chemiluminescence. For virus infection and co-immunoprecipitation, about 60% confluent cells in 100-mm tissue culture plates were infected with viruses at a multiplicity of infection of 10 plaque-forming units/cell. For virus transformation, 100-mm tissue culture plates were infected with viruses at a multiplicity of infection of 10 plaque-forming units/cell. Anti-CBP antibody brought down large T and small T antigens. Anti-CBP antibody brought down large T as well as CBP, whereas normal rabbit IgG did not. These co-immunoprecipitation results show that large T forms complexes with CBP in both mouse and rat transformed cells. Neither small T nor middle T was found in these complexes, although their presence may have a role in large T:CBP binding by directly or indirectly modifying large T or CBP. To test this possibility, the BR-IT cell line expressing only large T was examined. Large T was found to co-precipitate with CBP, showing that neither small nor middle T are essential for large T:CBP interaction. Py6, a polyoma-transformed 3T3 cell line expressing a C-terminally truncated large T along with middle and small T proteins, was negative, indicating that the aminoterminal fragment of large T (roughly, residues 1–350) does not bind to CBP (data not shown).

The region of SV40 large T containing the pRb-binding site has been found to be involved in CBP/p300 binding in some studies but not in others (28, 38). To determine whether a Py mutant large T unable to bind pRb (RB1) can still bind to CBP, extracts of NIH 3T3 cells infected with mutant RB1 or wild type virus were immunoprecipitated with anti-CBP antibody and blotted with anti-T antibody (Fig. 2). Anti-CBP antibody did not bring down the nonspecific cellular protein from the uninfected cell extracts (lane 2), which migrated at a slightly higher molecular weight position than large T by SDS-PAGE and which was detected in whole cell extracts by anti-T antibody (lanes 1 and 3). Control antibodies (normal IgG and anti-Rho GDI antibody) did not bring down either CBP or large T (lanes 4, 5, 8, and 9). Both wild type and RB1 mutant large T co-precipitated with anti-CBP antibody (lanes 6 and 10). Thus
**Co-immunoprecipitation experiments were also carried out using anti-T to precipitate and anti-CBP to blot. Results were variable in that CBP was not consistently detected (data not shown). This most likely reflects the fact that large T is more abundant than CBP and only a fraction of large T is bound to CBP. The bound fraction was estimated to be roughly 1–2% by comparing band densities of large T in input and co-IP lanes.**

**Py Large T Inhibits CREB-mediated Transactivation—**To determine whether large T binding to CBP/p300 has functional consequences, we studied the effect of large T on transactivation by CREB, which is positively regulated by CBP (Fig. 3). CBP/p300 proteins are co-activators of CREB. Adenovirus E1A is known to inhibit the transactivation activity of CREB (29). When CREB is phosphorylated at Ser-133 position by cyclic AMP-dependent protein kinase (PKA), it binds to CBP/p300 and activates transcription of its target genes. For these assays, the N-terminal region (amino acids 1–280) of CREB fused with the DNA binding domain of yeast GAL4 and a reporter plasmid (pFR-Luc) carrying 5xGAL4 binding sequences in the promoter region that controls expression of the luciferase gene were used. p300 or CBP expression plasmids together with the GAL4-CREB expression plasmid were co-transfected into NIH 3T3 cells (Fig. 3). Co-transfection of the p300 expression plasmid increased the activity of CREB, whereas co-transfection of equal amount of CBP expression plasmid increased the activity of CREB only slightly. It is not clear why p300 has more effect on CREB than on CREB expression plasmid on the activity of CREB in NIH 3T3 cells. Co-transfection of the large T expression plasmid suppressed the activity of the CREB transactivation by CBP/p300 in a dose-dependent manner. These results suggest that suppression of CREB transactivation by CBP/p300 may be mediated through sequestration of CBP/p300 from the phosphorylated CREB.

**Inhibition of CREB-mediated transactivation could result in principle from a direct interaction of large T with CREB. This was tested in co-immunoprecipitation experiments using anti-CREB-1 and anti-CREB-2 antibodies and extracts of BR-T cells expressing large T. Immune complexes were separated and blotted for large T. No evidence of large T co-precipitation was observed (data not shown), indicating that inhibition of transactivation results from large T binding to CBP/p300 co-activators and not to CREB.**

**CBP Binding and Inhibition of CREB-mediated Transactivation by Large T Occurs in the Absence of p53—**It has been reported that CBP/p300 interacts with p53 and activates p53-responsive genes such as those for p21<sup>wp1/vaf-1</sup> and mdm2 (13, 14). It is also known that SV40 large T forms a ternary complex with CBP/p300 and p53 (38). CBP/p300 may therefore play a role as a bridge between polyomavirus large T and p53.
performed transient transfection assays in p53−/− MEFs using the plasmids as described above (Fig. 4A). The reporter gene was activated 16-fold by co-transfection of RSV-PKA and Gal-CREB. It was further activated when CBP or p300 was co-transfected. In all cases, co-transfection of large T plasmid suppressed the transactivation activity of CREB in a dose-dependent manner.

To further test whether large T interacts with CBP in the absence of p53, we performed co-immunoprecipitation with cell extracts from large T transfected p53-null MEFs. The results showed that large T was found in the immune complexes with CBP precipitated with anti-CBP antibody (Fig. 4B). Thus, p53 is dispensable for large T-CBP interaction and for inhibition of CREB-mediated transactivation.

**Mutation of Large T Leads to Loss of CBP Binding and of Inhibition of CREB-mediated Transactivation**—To define the binding site of large T to CBP, mutations were introduced by site-directed mutagenesis into the “QLPP” sequence (residues 668–671) homologous to the regions in E1A and SV40 IT involved in p300/CBP binding (see Fig. 1A). The mutants were then tested in CREB-mediated transactivation assays (Fig. 5A). Mutations L669H and F670Y showed little or no change in inhibitory activity. However, substitutions for the proline at position 671, either P671L or P671C, knocked out the inhibitory function of large T in this assay. To confirm that the loss of inhibitory function is due to failure of the 671 mutants to bind CBP, co-immunoprecipitation experiments were carried out with wild type and mutant proteins. Cell extracts from NIH 3T3 cells transfected with wild type and mutant Py large T cDNAs were immunoprecipitated with anti-CBP antibody and blotted with anti-T monoclonal antibody (Fig. 5B). Wild type large T and L669H and F670Y large T mutant proteins were found in the immune complexes, whereas P671L and P671C were not detected. The levels of expression of the large T proteins were comparable in the cell extracts (Fig. 5C). The loss of inhibitory activity as well as binding activity in the 671 mutants defines this region of large T as essential for interaction with CBP.

**Differential Effects of Py Large T on CREB- and NF-κB-mediated Transactivation**—Many transcription factors are known to interact with CBP/p300. Among them, p65 is known to interact with CBP/p300. Among them, p65 is an NF-κB complex activator of target genes by binding to CBP/p300 (18). We tested by transient transfection assays whether large T inhibits NF-κB as well as CREB-mediated transactivation. The NF-κB and the CRE-Luc reporter plasmids have five copies of NF-κB and four copies of CRE binding sites, respectively. The transactivation of luciferase reporter gene in the CRE-Luc plasmid was inhibited by wild type Py large T and adenovirus E1A but not by the P671L mutant large T, which fails to bind CBP (Fig. 6A). The transactivation activity of NF-κB, however, was not inhibited by large T, though it was inhibited by adenovirus E1A (Fig. 6B). Py large T thus appears to function differentially on CBP target proteins. This contrasts with adenovirus E1A, which inhibits both of these CBP target proteins that are known to be regulated by E1A (18, 29). Similar reporter assays were performed with p53-Luc reporter plasmid carrying 15 copies of p53 binding sites. The results showed no inhibition of p53-dependent transactivation by polyoma large T (data not shown).

**CBP-binding Mutants Are Competent to Transform Cells in Vitro but Defective in Tumor Induction in Newborn Mice**—
Newborn mice were inoculated intraperitoneally with equivalent amounts of wild type virus strain PTA and the large T mutant PTA-P671L and followed for development of tumors as described (34). The results in Table I show that the mutant is severely restricted in its ability to induce tumors. This is seen in the lower fraction of animals affected and in the greater time required for tumors to develop. Significantly, only a single tumor type, subcutaneous fibrosarcomas, was seen in mutant-infected mice. These tumors developed only around the site of virus inoculation. Such tumors normally appear late and are therefore relatively rare in wild type virus-infected mice, which typically succumb earlier to various other tumors. The restricted pattern of tumor induction by the mutant suggests a primary block in virus replication. Preliminary observations indicate that PTA-P671L is indeed unable to amplify and cause a disseminated infection following inoculation of newborn mice (data not shown).

Although the 671 large T mutant is defective in inducing tumors, it may be able to transform cells normally based on retention of a normal middle T. This was tested by transfection of wild type and mutant viral DNAs into F-111 rat embryo fibroblasts. Transformation of these cells does not depend on the ability of the virus to replicate and can be regulated by middle T antigen alone (37). As shown in Table II, cells transfected by wild type and mutant DNAs gave rise to equivalent numbers of foci, indicating that loss of CBP binding by large T has no affect on transforming ability.

**DISCUSSION**

Polyomavirus large T antigen interacts with CBP/p300 and differentially regulates CBP/p300 target transcription factor-dependent transactivation. Adenovirus 12S.E1A, used as a control in this study, represses activation of CREB-, NF-κB-, and p53-dependent reporter genes, confirming earlier results (14, 18). In contrast, Py large T was found to inhibit only CREB-mediated transcriptional activation among these tar-
gets. Large T is known from other work to be unable to block p53 function (9, 41), but is apparently able to bypass the p53 cell cycle block through binding of pRB. Binding of E1A to the OH3 domain of CBP affects its ability to function as a coactivator in conjunction with some transcription factors and not others (21). In a similar manner, binding of large T to CBP may well affect its ability to function in certain transcription complexes and not others in others (42). CBP and p300 were originally identified as targets of CREB and adenovirus E1A, respectively (15, 43). They regulate diverse cellular responses such as cell cycle, differentiation, and apoptosis through interaction with many cellular factors that are involved in these biological functions. Despite their structural similarity, they can be distinguished based on regulation of genes involved in cell cycle inhibition and differentiation (44).

The CBP/p300 binding sequence of Py large T is homologous to those of SV40 large T and adenovirus E1A. Substitutions of the proline at position 671 of large T in this region of homology result in a loss of CBP/p300 binding and of the repressive activity of large T on CREB-mediated transactivation by CBP/p300. These mutants transform rat cells normally but fail to induce a broad spectrum of tumors in mice, suggesting a failure to replicate and spread in the intact host. Proline 671 substitution mutants grow poorly in normal NIH 3T3 cells but can be partially complemented for growth in mouse cells expressing wild type large T.\(^2\) These findings indicate that CBP/p300 binding by Py large T is essential for virus growth. Polyoma and SV40 viral DNAs are normally assembled in a highly acetylated chromatin (45). Binding of the co-activators by large T could be important in bringing associated histone acetyltransferase activities to the viral origin region (33), leading to the observed hyperacetylation of viral chromatin and aiding in transcription and replication of viral DNA (46). CREB is known to bind to CRE as a CREB-1 homodimer or CREB-2/ATF heterodimer (47). Binding of CBP/p300 and associated activities may also occur through a putative CREB-Pc-Jun-1 binding site (-TCAAGTCA-) that lies about 70 base pairs upstream of the VP2 transcription start site or other possible CRE sites in the Py enhancer (48–50).

The evidence that polyomavirus large T interacts with CBP and p300 raises the possibility that some cellular targets normally affected by these co-activators may be regulated by the virus. CREs are involved in regulating a wide variety of cellular and viral genes (51). This element is especially important in cancer cell growth inhibition. CRE decoy oligonucleotide inhibits CRE-dependent gene transcription in various cancer cells without adversely affecting normal cell growth (52). Cyclic AMP and various agonists are able to revert the phenotypes of many transformed cells toward a more normal appearance and behavior. Exposure of polyoma-transformed F-111 cells to forskolin, for example, inhibits the ability of these cells both to form foci and to grow in soft agar.\(^3\) The finding that the large T CBP/p300 binding mutants transform cells indicates that if inhibition of cyclic AMP-responsive genes occurs, this action of large T would have little or no discernible effect on the transformed phenotype, at least in cell culture.

The small T and middle T proteins of polyoma virus and SV40 might have effects opposite to that of large T on CREB regulation by virtue of their binding and inhibiting protein phosphatase 2A (53–55). SV40 small T binds and prevents PP2A from dephosphorylating CREB-P, thereby promoting its binding (56). Polyomavirus small T may function in the same manner on CREB. Transcriptional activation of the e-fos promoter has been shown to depend at least in part on polyoma-middle T activation of phosphatidylinositol 3-kinase signaling and the promoter proximal CRE (57). Further studies at the virus level will be necessary to understand these apparently opposing effects of the polyoma T antigens on CREB target genes.

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