The transcription factor Sp1 regulates the activity of a large number of eukaryotic gene promoters, including early SV40 and human immunodeficiency virus type 1 (HIV-1). Here, we report that expression of SV40 small tumor antigen (small t) in quiescent CV-1 cells transactivates two Sp1-responsive promoters, including a deletion mutant of HIV-1 LTR, through specific inhibition of endogenous AC and ABc forms of protein phosphatase 2A (PP2A). Expression of a small t mutant, lacking the PP2A-binding domain, failed to transactivate Sp1. Overexpression of the B56α, B56β, and B56γ regulatory PP2A subunits strongly inhibited the ability of small t, but not the phosphatase inhibitor, okadaic acid, to enhance Sp1-driven gene expression. Using inhibitors and co-expression of kinase-deficient mutants, we also show that functional phosphatidylinositol 3-kinase (PI 3-kinase) and atypical protein kinase C (PKCζ) are required for small t-induced Sp1-dependent promoter transcriptional activation. Moreover, two inhibitors of PI 3-kinase, wortmannin and LY294002, inhibit the initiation of SV40 DNA replication in quiescent CV-1 cells. Taken together, these results suggest that PP2A and PI 3-kinase contribute to the ability of small t to regulate Sp1 activity, stimulate early SV40 DNA replication, and enhance the transformation of resting cells during SV40 infection.

The nuclear transcription factor Sp1 is expressed in most mammalian cells and binds to GC-rich elements in the promoters of a wide variety of cellular and viral genes (1–3). Sp1 can undergo two major post-translational modifications, including glycosylation (4) and phosphorylation (5–7), that are believed to modulate its DNA-binding and -transactivating activities. Sp1 was first isolated as a transcription factor that binds to the GC-rich elements in the promoter of the beta-actin gene and participates in the regulation of many cellular processes, including metabolism and division (8). The SV40 early gene encodes two proteins: the small tumor antigen (small t) and large tumor antigen (large T). Sp1 interacts with the large T during infection of the permissive monkey kidney CV-1 cells (12). During infection of the permissive monkey kidney CV-1 cells, nearly all of the host’s protein phosphatase 2A (PP2A) becomes complexed with SV40 small t (13). PP2A, a predominant protein serine/threonine phosphatase in most mammalian cells, participates in the regulation of many cellular processes, including metabolism and division (14). The core enzyme is a dimeric complex consisting of a catalytic subunit (C) bound to a subunit (A), that can associate with a third polypeptide termed “B” or the phosphatase regulatory (PR) subunit.

The PP2A regulatory subunits are categorized into several distinct families that generate a diversity of holoenzymes (14, 15). Besides regulating phosphatase activity, the B subunits are thought to be responsible for the substrate specificity and targeting of PP2A (14–16). We have reported that SV40 small t is able to associate with endogenous PP2A and inhibit phosphatase activity in transfected monkey kidney CV-1 cells (17). Interaction of small t with PP2A promotes the growth of quiescent cells through stimulation of a signaling cascade involving phosphatidylinositol 3-kinase (PI 3-kinase), atypical protein kinase C ζ (PKCζ), and the mitogen-activated protein kinase kinase/extracellular signal-regulated kinase kinase (17, 18). Moreover, SV40 small t forces quiescent cells to re-enter the S phase of the cell cycle and stimulates SV40 DNA replication in CV-1 cells (19). Small t also regulates the cyclic AMP-response element-binding protein (20), AP-1 (21), NF-κB (18), and serum response element-regulated promoters (21) in a PP2A-dependent fashion. All of these cellular effects of small t may explain its “helper” function during SV40 infection.

Besides SV40, human immunodeficiency virus type 1 (HIV-1) long terminal repeat (LTR) is one of the numerous viral promoters tightly regulated by Sp1 (22, 23). Incubation of T lymphocytes with okadaic acid, an inhibitor of type 1 and 2A protein phosphatases (24), induces the phosphorylation of Sp1 and activation of Sp1-dependent HIV-1 gene transcription (25). Taken together, these findings prompted us to investigate whether interaction of small t with PP2A leads to up-regulation of Sp1 activity. We show here that expression of SV40 small t in quiescent CV-1 cells induces transactivation of two Sp1-dependent promoters through specific inhibition of endogenous PP2A activity. We also demonstrate that PI 3-kinase and PKCζ are required for the transactivating effects of small t. Last, we show that inhibition of PI 3-kinase significantly delays the initiation of SV40 DNA replication during infection of CV-1
cells. Thus, in addition to providing evidence for a novel role for PI 3-kinase during SV40 infection, our results reveal PP2A enzymes and PI-3 kinase to be novel intracellular regulators of Sp1-dependent gene expression.

EXPERIMENTAL PROCEDURES

Plasmids and Reagents—Plasmids utilized in this study included the following: pCMV-HIVS(−84)luc and pG3-CAT (25); SR-A-AP55 (26); pCMV5-small t and pCMV5-small t mutant 3 (17); pCEP-4 plasmids for expression of the B56α, B56β, and B56γ regulatory subunits of PP2A (16), pCMV5-ERK2-Y185P (27); and pCECMV-PP2Ac (28). Wortmannin and okadaic acid were purchased from Sigma, and LY294002 was purchased from Calbiochem.

Cell Culture, Transfection, and Treatment—Monkey kidney CV-1 cells (American Type Culture Collection) or CV-1 cells stably expressing SV40 wild-type small t (18) were maintained at 5% CO2 in Dulbecco’s modified Eagle’s medium containing 10% calf serum (HyClone). Subconfluent cell cultures were transiently transfected with the indicated plasmids using LipofectAMINE, according to the manufacturer’s instructions (Life Technologies, Inc.) and as described previously (18). Transfections were carried out at a constant amount of DNA, and duplicate or triplicate dishes of cells were used for each set of transfected plasmid. Under our experimental conditions, we found no statistical differences in the transfection efficiency between distinct sets of cells within one experiment. Cells were serum-starved 24 h post-transfection by incubation for 20 h in Dulbecco’s modified Eagle’s medium containing 2% dialyzed fetal bovine serum (HyClone). Cells were then left untreated or incubated for 3–5 h with the appropriate agents (okadaic acid, wortmannin, or LY29402) in the same medium.

Luciferase and CAT Reporter Gene Activity Assays—Luciferase activity was determined 48 h post-transfection using the Luciferase Assay System kit from Promega, as described previously (18). Luciferase activity was measured in duplicate aliquots (20 μl) of total cell extracts by measuring for 10 s the light emission in an OptiComp luminometer. CAT activity was measured 48 h post-transfection in 40 μl of total cell extract following exactly the procedures described previously (25). The luciferase and CAT activities were normalized to the protein concentration determined in the same sample using a Bio-Rad protein assay.

Analysis of SV40 Infection—Subconfluent CV-1 cells (100-mm dishes) were infected with 0.5 ml of plaque-purified wild-type SV40 virus (strain 776) at a multiplicity of 3–5 plaque-forming units/cell. Ten dishes were infected with 0.5 ml of medium containing 0.2% serum with or without 100 nM wortmannin were added to the cells 2 h postinfection. At the indicated time postinfection, the viral DNA was extracted according to the protocol of Hirt (29). The purified viral DNA from approximately one-fifth of a 100-mm dish of infected cells was digested with BamHI, fractionated on 1% agarose gel, and blotted on Hybond-N nylon membranes. Blots were hybridized with total 32P-labeled SV40 DNA.

RESULTS

Expression of SV40 Small t in CV-1 Cells Transactivates Sp1-Responsive Promoters—We first performed reporter gene assays in transfected CV-1 cells to address the possibility that SV40 small t induces Sp1-driven promoter activation. CV-1 cells were co-transfected with pCMV5 alone or pCMV5 plasmids encoding wild-type or mutant small t proteins, together with Sp1-responsive luciferase or CAT reporter constructs. The transfected cells were serum-starved, after which total extracts were prepared and assayed for luciferase or CAT activity. As shown in Fig. 1A, expression of wild-type small t resulted in a ~7-fold increase in the activity of HIVS(−84)luc, a luciferase reporter construct under the control of a mutant of HIV-1 LTR deleted from all sequences upstream of three Sp1 sites (25). The effects of wild-type small t could be mimicked by incubating control cells with the PP2A inhibitor okadaic acid, which produced a 12-fold induction of luciferase activity. In contrast, expression of a truncated form of small t (mutant 3) lacking the PP2A-binding domain (17) failed to induce these transactivating effects. Comparable results were obtained in cells transiently transfected with pG3-CAT (25), an artificial plasmid containing the CAT gene driven by the TATA box of the adenovirus major late promoter coupled to three Sp1 motifs (Fig. 1B). Okadaic acid treatment and expression of wild-type small t, but not mutant 3, resulted in a ~10- and ~5-fold increase in CAT activity relative to control cells, respectively. Control experiments showed that the basal activity of each corresponding HIVS(−84)luc or pG3-CAT constructs deleted from the three Sp1 sites was not affected by okadaic acid, as reported previously (25), or by small t proteins (data not shown).

SV40 Small t Up-regulates Sp1-Dependent Promoter Activity through Selective Inhibition of Endogenous PP2A Enzymes—AC dimers and ABαC holoenzymes account for the majority of PP2A activity in CV-1 cells, whereas AC-small t heterotrimers are the prevalent PP2A species in SV40-infected and SV40 small t-transfected CV-1 cells (13, 17). The AC-small t complexes appear to be relatively unstable, since they can dissociate and reform in cellular extracts (13). Small t can directly bind to free AC dimers and, at least in part, displace Bα from ABαC holoenzymes, resulting in subsequent inhibition of PP2A activity in CV-1 cells. However, residual AC and ABαC enzymes are still present in small t-expressing cells (17). The inability of small t mutant 3 to promote Sp1-driven promoter transactivation (Fig. 1) suggested that the effects of SV40 small t were dependent on its interaction with PP2A. To further substantiate this assumption, and because the B56(25) is used as a control because B56(25) regulatory subunits of PP2A can compete in vitro with small t for binding to the AC core enzyme (15), we compared the effects of overexpressing various B56 regulatory subunits on small t-dependent Sp1 transactivation. CV-1 cells stably expressing wild-type small t were co-transfected with HIVS(−84)luc and plasmids encoding the three different iso-
forms ($\alpha$, $\beta$, and $\gamma_1$) of the B56 family of PP2A regulatory subunits (for nomenclature, see Ref. 28). As shown in Fig. 2, expression of either B56$\alpha$, B56$\beta$, or B56$\gamma_1$ suppressed the induction of HIV5(-84)luc by small t. Significantly, these inhibitory effects could be reversed by incubating B56-transfected cells with okadaic acid, suggesting that overexpressed B56 subunits down-regulated Sp1-driven promoter activity by altering the levels of endogenous PP2A activity. Together, these findings support a role for PP2A in small t-dependent Sp1 regulation. They also provide the first evidence that changes in the intracellular subunit composition of PP2A can differentially affect Sp1-dependent gene activity.

SV40 Small t-induced Transactivation of Sp1-responsive Promoters Requires Functional PI 3-Kinase and PKC $\zeta$—We have reported that two bifunctional signaling pathways involving PI 3-kinase (p110-p85$\alpha$) and PKC $\zeta$ mediate the activation of the mitogen-activated protein kinase cascade and NF-κB by small t in CV-1 cells (18). To analyze the participation of PI 3-kinase in the regulation of Sp1, small t-expressing cells were transfected with the reporter construct alone. Values shown are the mean ± S.D. of duplicate assays from four separate experiments.

Inhibition of PI 3-Kinase Delays Early Viral DNA Replication in SV40-infected CV-1 Cells—Stimulation of Sp1 upon SV40 infection of CV-1 cells leads to enhanced expression of SV40 viral and cellular promoters (6, 8). By compromising the ability of small t to transactivate NF-κB (18) and Sp1 (Fig. 3), PI 3-kinase may play a key role during SV40 infection. To test this hypothesis, we analyzed the initiation of SV40 DNA replication in CV-1 cells infected with viral particles. As described under "Experimental Procedures," after viral adsorption, cells were cultured in the presence of 0.2% serum, in the absence or presence of either LY294002 or wortmannin. Under these experimental conditions, and at the time periods examined (19–36 h postinfection), the infected CV-1 cells were in a quiescent state, as confirmed by parallel experiments measuring [3H]thymidine incorporation (data not shown). The viral DNA was purified from the infected cells and analyzed by Southern blot. Fig. 4 shows that the levels of newly replicated SV40 DNA detected 20 h postinfection in control, untreated CV-1 cells were reduced in infected cells that had been incubated with 100 nM wortmannin or 100 μM LY294002. We also found that, in the time period examined, treatment of cells with wortmannin or LY294002 did not affect cellular viability, and equivalent numbers of cells were recovered from untreated or treated cells in each experimental condition. Thus, inhibition of early SV40 DNA synthesis by wortmannin or LY294002 cannot be attributed to putative cytotoxic effects of these compounds. These results strongly suggest that PI 3-kinase-dependent mechanisms regulate the early phase of SV40 DNA replication.

**Discussion**

We have previously reported that, in quiescent CV-1 cells, interaction of SV40 small t with endogenous AC and ABc forms of PP2A (17) activates HIV-1 LTR and NF-κB, and these effects are dependent on both functional PI 3-kinase and PKC $\zeta$ (18). Since both NF-κB and Sp1 regulate HIV-1 LTR activity (22), we investigated here the effects of small t, PI 3-kinase, and PKC $\zeta$ on Sp1 regulation. We first show (Fig. 1) that small t and okadaic acid induce Sp1 transcription in CV-1 cells. Significantly, okadaic acid has similar effects in J. Huan cells (25). Consistent with a specific involvement of PP2A in Sp1 regulation, all three B56 ($\alpha$, $\beta$, $\gamma_1$) regulatory subunits of PP2A counteracted the transactivation of Sp1 induced by small t, but not okadaic acid (Fig. 2). When present in excess, B56 regulatory subunits of PP2A can displace small t from AC-small t complexes in vitro (15). We therefore propose that, following overexpression of B56, the displacement of small t and subsequent formation of AB56C heterotrimers simply reverse PP2A inhibition by small t. Interestingly, in CV-1 cells, AC and ABc are present in both cytoplasm and nuclear subcellular compart-

**Fig. 2.** Overexpression of B56 regulatory subunits of PP2A inhibit SV40 small t-induced Sp1 transactivation. CV-1 cells (60-mm dishes) stably expressing SV40 wild-type small t were transfected with 1 μg of HIV5(-84)luc and 4 μg of pCMV5 (C), pCEP4-B56$\alpha$ (B56$\alpha$), pCEP4-B56$\beta$ (B56$\beta$), or pCEP4-B56$\gamma_1$ (B56$\gamma_1$). Cells were serum-starved and left untreated (black bars) or incubated for 3 h with 100 nM okadaic acid (OA) (hatched bars). Cells were then lysed and analyzed for luciferase activity. Results are expressed as the percentage of the mean normalized luciferase activity measured in extracts from quiescent small t-expressing cells transfected with the reporter construct alone. Values shown are the mean ± S.D. of duplicate assays from three separate experiments.

**Fig. 3.** Effects of inhibitors of PI 3-kinase, PKC $\zeta$, and ERK2 on SV40-small t-induced Sp1 transactivation. CV-1 cells (100-mm dishes) stably expressing SV40 small t were transfected with 2 μg of HIV5(-84)luc and 10 μg of pCMV5 (Control), SBE-Δp85 encoding a mutant of PI 3-kinase p85$\alpha$ regulatory subunit (Δp85$\alpha$), pRcCMV-ΔPKC$\zeta$ encoding a kinase-defective mutant of PKC $\zeta$ (PKC $\zeta$mut), or pCMV5-ERK2-Y185F encoding kinase-deficient ERK2 (ERK2-Y). Cells were then serum-starved and processed for luciferase activity assays. 

- Wortmannin
- LY294002
- B56mut
- ERK2-Y
AB56 and AB56βC are concentrated in the cytoplasm, and AB56γIC is targeted to the nucleus (15–17). Results from our overexpression studies imply that both cytosolic and nuclear forms of PP2A have the potential to regulate Sp1, either directly or indirectly. Thus, any alterations in the subcellular distribution and ratio between the endogenous AC core enzyme and PP2A holoenzymes could affect Sp1-dependent promoter transactivation. Beside PP2A, we have identified PI 3-kinase and type-specific PKC ζ as novel regulators of Sp1-responsive promoter activity in CV-1 cells (Ref. 18 and Fig. 1). Although not presented here, we found similar results in mouse NIH 3T3 and human J. Dhan cells, suggesting that the regulatory mechanisms described in CV-1 cells are not restricted to this unique cell type. The existence of a nuclear pool of PKC ζ in CV-1 cells suggests that PKC ζ could directly regulate Sp1. Indeed, PKC ζ has been recently reported to bind to and phosphorylate the zinc finger region of Sp1 in vitro and in carcinoma cell lines (32).

Our findings are clearly important for understanding the biology of SV40. First, small t transactivates SV40 early and late promoters (33). Next, injection of CV-1 cells with SV40 leads to a ~10-fold increase in the intracellular levels of Sp1 mRNA and proteins, and this effect can be attributed to expression of an early viral protein (8). Since Sp1 stimulates the activity of the SV40 early promoter, its enhanced expression may be critical for the viral life cycle (1). Mutant SV40 viruses that lack small t antigen replicate less efficiently than the wild-type virus, and microinjection of small t in CV-1 cells that lack small t antigen replicate less efficiently than the wild-type virus, and microinjection of small t in CV-1 cells (Ref. 18 and Fig. 1) implies that transactivation of NF-κB mutant viruses (19). In agreement with these observations, we found that overexpression of distinct PP2A subunits differentially deregulates Sp1-dependent HIV-1 LTR activity (Fig. 2) support these findings. We have demonstrated that, following expression of small t, PI-3 kinase-dependent activation of PKC ζ induces transactivation of NF-kB-responsive promoters, including HIV-1 LTR (18). Remarkably, the cooperative interaction between NF-kB and Sp1 is crucial for transcriptional activation of HIV1-LTR (45). Moreover, induction of Sp1 during cytomegalovirus infection mediates up-regulation of NF-kB promoters (46). Indeed, Sp1 directly interacts with NF-kB-binding sites, providing a means to keep basal levels of NF-kB-dependent gene expression elevated in the absence of activated NF-kB (47). By regulating both NF-kB and Sp1, the signaling involving PP2A, PI 3-kinase, and PKC ζ may play a critical role in the transcriptional regulation of not only SV40 but also HIV-1 promoters. Results obtained with small t suggest that deregulation of this signaling may be strategically targeted by viruses to elevate viral and cellular gene expression during infection of resting cells.

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Protein Phosphatase 2A and Phosphatidylinositol 3-Kinase Regulate the Activity of Sp1-responsive Promoters
Alphonse Garcia, Silvia Cereghini and Estelle Sontag

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