p300 Collaborates with Sp1 and Sp3 in p21<sup>wt/cip1</sup> Promoter Activation Induced by Histone Deacetylase Inhibitor*

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We have reported that histone acetylation induced by trichostatin A (TSA) promotes p21<sup>wt/cip1</sup> (p21) expression, the GC-box located just upstream of TATA box was responsible for TSA-induced promoter activation, and both Sp1 and Sp3 were the working activator of this GC-box. To understand the molecular pathway from histone acetylation to this Sp1 family factors-mediated promoter activation, we investigated the function of p300, one of the histone acetyltransferase, in the present work. The evidence supporting the linkage between p300 and TSA-induced p21 promoter activation were realized from the following findings: 1) cotransfection of p300 elevated p21 promoter activity, and this elevation was dependent on TSA-responsive GC-box; 2) TSA-induced promoter activation was blocked by the introduction of p300 dominant-negative mutant into cells; and 3) Sp1- or Sp3-mediated activation was also suppressed by this p300 dominant-negative mutant. Our data also suggested that p300 collaborates with Sp1 in a way which is different from that when p300 collaborates with p53 in p21 transcription.

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1 The abbreviations used are: p21, p21<sup>wt/cip1</sup>; TSA, trichostatin A; DBD, DNA binding domain; AD, activation domain; bp, base pair; PMSF, phenylmethylsulfonyl fluoride.

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hybrid experiments, the following constructs were used. 1) pG5luc was a 5-GAL4 DNA binding sites-containing firefly luciferase vector (Promega). 2) pGAL4p300 was the same construct as mentioned above, which is a chimeric fusion of GAL4 DNA binding domain (DBD) and full-length p300 cDNA. 3) pVP16pCAF was created by inserting the EagI fragment of pCAG-CAT DNA into pCI-pCAF vector (Promega), which has a VP16 activation domain (AD) sequence, at NotI and KpnI sites. 4) pVP16Sp1N was made by two steps. The 1.5-kilobase BanHI fragment of Sp1 cDNA from pCGN-Sp1 was inserted into pcDNA3.1/Myc.HisC vector at the BanHI site first, and then the EcoRV and KpnI insert from correctly directed clone was subcloned into pACT vector at the EcoRV and KpnI sites. 5) pVP16Sp1C was made by the same strategy as that for pVP16Sp1N except the 0.5-kilobase BanHI fragment of Sp1 cDNA was used, and 6) pRL-TK as mentioned above.

Transfection and Luciferase Assay—Cells were seeded into 48-well plate at a density of 30,000 cells/well the day before transfection. In the transfection experiments with reporter plasmid only, HeLa cells were transfected with 100 ng of promoter-reporter construct by standard calcium phosphate procedure. Treatments of TSA were started after 24 h and continued for another 24 h generally, except where noted in the figure legends. In cDNA cotransfection experiments, transfection was performed by using Fugene™6 (Roche Molecular Biochemicals). The DNA mixture contained 20 ng of reporter and 20–100 ng of cDNA and either pCGN or pcDNA3.1 to adjust a total amount of DNA to 120 ng per well. For mammalian two-hybrid assays, COS-1 cells were transfected by standard calcium phosphate procedure with the combination of pG5luc, pGAL4, and pVP16 (or their corresponding fusions) in 1:1:1 molar ratio. pGEM-S2Zf(+) vector was also added as carrier and for making the concentration of DNA to 0.3 μg/well. In all of these experiments, after 2 days of transfection, 5 of 50 μl of total cell lysate was used, and its luciferase activity was assayed by luminometer and dual luciferase assay kit (Promega). The luciferase activities were normalized against the activity of PRL-TK control vector (Promega) and protein concentration. Every experiment was performed at least three times.

Immunoprecipitation Pull-down Assays—Labeled proteins were produced from pGAl4p300, pCl-pCAF, and pcDNA3.1/Myc.HisC plasmid with in vitro transcription and translation system (TNT kit, Promega) in the presence of [35S]methionine. Two μl of in vitro translated 35S protein and 2 μg of specific antibody were incubated in 50 μl of binding buffer (25 mM Tris-HCl (pH 8.0), 10% glycerol, 75 mM KCl, 5 mM MgCl2, 0.1 mM EDTA, 0.1% Nonidet P-40, 0.5 mM dithiothreitol, 0.5 mM PMSF) at 4°C for 1 h and with 10 μl of 3% bovine serum albumin-blocked protein G-Sepharose (Amersham Pharmacia Biotech, 50% slurry) for an additional 1 h. After washing with binding buffer three times, the beads were resuspended in 50 μl of the same buffer and incubated with 2 μl of labeled pCAF or Sp1 reaction mixture at room temperature for 30 min. Then the beads were washed again and boiled for 2 min in the presence of 20 μl of Laemmli buffer. Finally, the supernatants were separated on 8% SDS-polyacrylamide gel electrophoresis gel. For the immunoprecipitation of unlabeled cellular p300 protein, HeLa cell lysates in radioimmune precipitation buffer (25 mM Tris-HCl (pH 8.0), 150 mM NaCl, 1% Nonidet P-40, 0.5% deoxycholate, 0.1% SDS, 2.5 mM EDTA, 1 mM dithiothreitol, 0.5 mM PMSF) were immunoprecipitated with anti-p300 antibody and protein G-Sepharose. The beads were washed by radioimmune precipitation buffer three times and binding buffer once. Thereafter, the beads were used for pull-down assay as described above.

Electrophoretic Mobility Shift Assay—The experimental procedure was the same as that described previously (10) except that the nuclear extract was from HeLa cells, and only the 32P-labeled oligonucleotides probe with the wild type p21 promoter sequence (−40 to −10 bp from TATA box) was used. The polyclonal antibodies directed against Sp1 (catalogue number sc-59), Sp3 (sc-644), p300 N-terminal (p300-N, sc-584), p300 C-terminal (p300-C, sc-585) were purchased from Santa Cruz Biotechnology (Santa Cruz, CA). The monoclonal antibody for p300 (p300-mono, 05–267) was from Upstate Biotechnology (Lake Placid, NY).

RESULTS

Sp1/Sp3 Up-regulate p21 Promoter Activity through a TSA-responsive GC-box—We have reported that TSA greatly induced the p21 promoter activity and determined the cis-element responsive to TSA in NIH 3T3 cells (10). We found that these results are not cellular-specific. In HeLa cells, the morphological differentiation and elevated p21 expression were also noticed after TSA treatment, and the minimal promoter region and TSA-responsive GC-box were the same as those in NIH 3T3 cells (results not shown). To confirm the functional effects of Sp1 family transcription factors on p21 promoter, especially on the TSA response of this promoter, we cotransfected wild type or the TSA-responsive GC-box-mutated promoter-luciferase constructs with Sp1 or Sp3 cDNA expression constructs into HeLa cells (Fig. 1). While Sp1 and Sp3 can obviously activate wild type minimal promoter (pRL21–60) in a dose-dependent manner, they poorly activate the GC-box mutated minimal promoter (pRL21–4) and their parent vector (pRL-null), respectively. Relative luciferase activity was derived from comparing the activities in the presence of Sp1 or Sp3 expression construct with the activity in the presence of the same amount of parental vector DNA. Values come from one of five separate experiments and represent the average of three samples with standard deviation.

FIG. 1. Activation of p21 promoter by Sp1 and Sp3 is dependent on the GC-box response to TSA. Indicated amounts of Sp1 or Sp3 cDNA expression constructs were cotransfected with wild type p21 minimal promoter (pRL21–60), GC-box lost mutant (pRL21–4), and their parent vector (pRL-null), respectively. Relative luciferase activity was derived from comparing the activities in the presence of Sp1 or Sp3 expression construct with the activity in the presence of the same amount of parental vector DNA. Values come from one of five separate experiments and represent the average of three samples with standard deviation.

p300 Participates in TSA-induced p21 Promoter Activation—Because no changes in Sp1/Sp3 protein expression or in their DNA binding activity were found after TSA treatment (data not shown), we considered that TSA-induced p21 promoter activity may result from some kinds of interaction between Sp1/Sp3 and histone acetyltransferase or deacetylase. As the first step to issue this question, we examined the effect of p300 on p21 promoter. As shown in Fig. 2, transfection of wild type p300 expression construct, pGAl4p300, into cells enhanced either full-length (pGL3b-4542) or minimal promoter (pGL3b-60) activity. The experiments performed using the intact wild-type p300 (pCMVβp300 provided from Prof. David M. Livingston) gave results similar to those using the GAL4 derivative (data not shown). This suggested the positive effect of p300 on p21 transcription. Different from p21 wild type minimal promoter, the activity of the GC-box mutated promoter (pGL3b-4) was not affected by p300 cotransfection. Thus the TSA-responsive GC-box is also required for the function of p300 to the p21 promoter, as it is required for the function of Sp1/Sp3 on p21 promoter.
The interrelationship of p300 and TSA-induced promoter activation was further evidenced by cotransfection of a dominant-negative mutant of p300 expression construct (pGAL4p300/1514–1922) with p21 promoter construct, followed by TSA treatment. The product of pGAL4p300/1514–1922 encodes only a small portion of p300 protein, corresponding to the CH3 domain and its surroundings, and has been reported to be capable of interfering with the activity of endogenous protein (28, 30). In our experiment, this mutant lost the up-regulating effect of wild type p300 on the p21 promoter (Fig. 3A). Meanwhile, in the cells expressing this mutant p300, the p21 minimal promoter activity induced by TSA was obviously dose-dependent suppressed (Fig. 3B). These results suggest that the p300 molecule is also involved in TSA-induced p21 promoter activation.

p300 and Sp1/Sp3 in p21 waf1/cip1 Promoter

The interrelationship of p300 and TSA-induced promoter activation was further evidenced by cotransfection of a dominant-negative mutant of p300 expression construct (pGAL4p300/1514–1922) with p21 promoter construct, followed by TSA treatment. The product of pGAL4p300/1514–1922 encodes only a small portion of p300 protein, corresponding to the CH3 domain and its surroundings, and has been reported to be capable of interfering with the activity of endogenous protein (28, 30). In our experiment, this mutant lost the up-regulating effect of wild type p300 on the p21 promoter (Fig. 3A). Meanwhile, in the cells expressing this mutant p300, the p21 minimal promoter activity induced by TSA was obviously dose-dependent suppressed (Fig. 3B). These results suggest that the p300 molecule is also involved in TSA-induced p21 promoter activation.

p300 Is Required for Sp1- or Sp3-mediated Transactivation of p21 Promoter—Considering the facts that both Sp1/Sp3 and p300 can up-regulate p21 promoter and function through the same GC-box in TSA-induced p21 promoter activation, the cooperative relationship between them might be present. To expose the interrelationship of Sp1/Sp3 and p300, we investigated the requirement of p300 for Sp1/Sp3-mediated transactivation. When Sp1 or Sp3 was cotransfected with various amounts of dominant negative mutant p300, Sp1/Sp3-mediated promoter activation was dose-dependent blocked (Fig. 4). This result suggests that p300 is required for Sp1/Sp3-mediated p21 transcription and that some kind of collaboration between p300 and Sp1/Sp3 was present during this process.

p300 Does Not Directly Interact with Sp1 in Vitro and in Vivo—The cooperation of p300 and Sp1/Sp3 shown in functional assays described above may be from direct or indirect interaction of p300 with Sp1/Sp3. As p300 has been shown to physically interact with various transcription factors, we examined the physical relationship between p300 and Sp1 in vitro and in vivo. Fig. 5 showed the results from two kinds of in vitro protein binding assays. In immunoprecipitation pull-down assay (Fig. 5A), the positive control, recombinant pCAF protein, can associate with recombinant p300 (lane 4) or native p300 (lane 7), whereas recombinant Sp1 cannot (lanes 5 and 8). That Sp1 does not associate with p300 in vitro was also implied from super shift assay (Fig. 5B). In this experiment, three kinds of antibodies for p300 failed to produce any shift or the loss of Sp1 and Sp3 complexes which were binding to the TSA-responsive GC-box-containing oligonucleotides (lanes 4–6). To examine whether there is the physical interaction between p300 and Sp1 in cellular situation, mammalian two-hybrid assay was performed. Fig. 6A shows the structures of fusion proteins produced in transfected cells and the schematic representation of this two-hybrid system. Briefly, after cotransfecting the GAL4 binding sites-containing reporter construct with GAL4DBD-fused vector as well as VP16AD-fused vector, the luciferase activity induced was detected. As shown in Fig. 6B, when the GAL4DBD-fused p300 protein expressed together with the VP16AD-fused pCAF protein, which is a known p300 association protein, the luciferase activity in cells increased more than 2-fold. However, when the GAL4DBD-fused p300 expressed with VP16AD-fused Sp1, neither its N-terminal nor C-terminal portion, the luciferase activity was not affected compared with that with VP16AD only. This means that the exogenous p300 and Sp1 did not interact directly in this system. In vivo co-immunoprecipitation was also tried to detect the interaction of endogenous p300 and Sp1, but no positive clue was found (data not shown).
DISCUSSION

The original purpose of this work is to elucidate how TSA affected Sp1-mediated p21 transcription. In view of recent progress in transcriptional regulation, we assumed that some kinds of histone acetyltransferase and/or deacetylase may be altered physically or functionally during TSA treatment and thus influence function of Sp1 family transcription factors. In working to try to identify these involved histone acetyltransferase and/or deacetylase, we found that p300, one of the histone acetyltransferases, up-regulates p21 promoter and functions through the GC-box responsible to TSA (Figs. 2 and 3). The dominant negative mutant of p300 can clearly block TSA-induced p21 activation, further supporting the opinion that p300 functionally contributes to TSA-induced p21 activation.

It has been reported that p300 works as a coactivator for various transcription activators, such as MyoD, p53, RAR, CREB, c-Jun, and for basal transcription factors, for example TBP (21–23). There is no report up to now implying the interaction of p300 and Sp1 family transcription factors. The same GC-box dependence of Sp1/Sp3 and p300 in p21 promoter activation reported in our present work, thereby, raises the pos-

**Fig. 3.** Dominant-negative p300 blocks TSA-induced p21 activation. A, p300/1514–1922 functions as a dominant negative mutant for p21 transcription in HeLa cells. Indicated amounts of pGAL4p300 or pGAL4p300/1514–1922 were cotransfected with p21 promoter pGL3b-60. (−) refers to the control cotransfected with pcDNA3.1, which is the parental vector of pGAL4p300 and pGAL4p300/1514–1922, and pGL3b-60. B, cells were transfected with 50 ng/well pGL3b-60 and different amounts of pGAL4p300/1514–1922, followed by 24-h TSA treatment. Values represent the average of five samples and standard deviation. Three separate experiments were performed.

**Fig. 4.** Dominant-negative p300 suppresses Sp1/Sp3-mediated p21 activation. Various amounts of pGAL4p300/1514–1922 were introduced into cells with pCGN-Sp1 or pCGN-Sp3, as well as p21 promoter. Relative luciferase activity of cell lysate was measured after 48 h. Values represent the average of five samples and standard deviation. Three separate experiments were performed.

**Fig. 5.** p300 does not directly interact with Sp1 in vitro. A, immunoprecipitation pull-down assays. [35S]methionine-labeled p300, pCAF, and Sp1 were made by in vitro transcription/translation (lanes 1–8), whereas cold p300 was from unlabeled HeLa cells (lanes 7 and 8). 10% of individual 35S-protein was directly loaded on gel and referred to as input (lanes 1–3). For immunoprecipitation, 35S-p300 (lanes 4 and 5), 35S-Sp1 (lane 6), or cold native p300 (lanes 7 and 8) were precipitated from in vitro translation mixture or cell lysate by specific antibodies and then mixed with 35S-pCAF (lanes 4 and 7), 35S-Sp1 (lanes 5 and 8), and 35S-p300 (lane 6), respectively. After binding incubation, the beads were washed and the precipitated proteins were separated by 8% SDS-polyacrylamide gel electrophoresis gel. B, super-shift assay. 32P-labeled double-stranded oligonucleotides with the TSA-responsive GC-box-containing sequence of the p21 promoter, HeLa cell nuclear extracts, and indicated antibodies were incubated together, and the reaction mixtures were loaded on 4% acrylamide gel and separated. The antibodies used were: anti-Sp1 (lane 2), anti-Sp3 (lane 3), anti-p300(N) (lane 4), anti-p300 (C) (lane 5), and anti-p300(mono) (lane 6).
sibility that p300 may cooperate with Sp1 family transcription factors as well.

To address this question, the dominant negative mutant of p300 was cotransfected with Sp1 or Sp3 based on the idea that if the cooperative relationship is present, cellular knockout of p300 will abolish the function of Sp1/Sp3. Our results support this idea (Figs. 3 and 4). Owen, et al. (31) reported recently that progesterone regulates transcription of p21 gene through Sp1 and CBP/p300. They showed data indicating that progesterone regulates p21 promoter activity through a Sp1 site and E1A can abolish the effect of progesterone on p21 promoter containing this Sp1 site. Given that other proteins except CBP/p300 also associate with E1A (32–34), we think the result from cotransfecting with E1A may not be enough for supporting the involvement of p300 in this Sp1 site-mediated transcription. By comparing the different effect of p300 on wild type or GC-box-mutated promoter and utilizing its dominant negative mutant to suppress TSA- and Sp1/Sp3-induced transactivation, we provide direct evidence here that p300 can regulate the activity of the p21 promoter through Sp1-mediated transactivation.

p300 is also involved in p21 transcription through a p53-mediated way (22, 30). In that case, p300 physically interacts with p53 and is recruited by p53 to the basal transcription machinery. However, the molecular basis of the collaboration of p300 and Sp1 in p21 promoter regulation seems different. As the results from in vitro and in vivo experiments failed to provide any evidence that p300 directly interact with Sp1 (Figs. 5, 6), we considered that p300 and Sp1 might indirectly interact through a common multi-protein complex which is important for p21 transcription. Given that either p300 or Sp1 can interact with TBP and other basal transcription factors (35–37), and that the Sp1 binding site in p21 promoter is so close to TATA box, this multi-protein complex might be the transcription initiation complex. Thus, we propose one hypothesis here, that the functional collaboration of p300 and Sp1 in p21 expression may rely on the effect of p300 on the activity of the initiation complex or the interaction of this complex with Sp1, which is the base for Sp1-mediated transcription in p21 activation. In fact, a multi-protein transcriptional complex containing TATA-binding protein, Sp1, and cAMP-response element-binding protein (CBP/p300) has been noticed recently (29). We prefer to say, based on the results presented here, that p300 is an indispensable factor for the p21 promoter activation, not only in a p53-mediated, DNA damage-responsible way but also in Sp1-mediated, basal and histone acetylation-effected way. Further work remains to be done to identify more details about the cooperation of p300 and Sp1.

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Fig. 6. p300 does not directly interact with Sp1 in mammalian two-hybrid system. A, schematic representation of the two-hybrid system. The full-length p300 was cloned into a GAL4DBD-containing vector; the almost full-length of pCAF or indicated regions of Sp1 were inserted into a VP16AD-containing vector. Both of them were cotransfected with a GAL4 DNA binding sites-containing luciferase reporter vector. B, luciferase activity induced by different combinations of cotransfection. COS-1 cells seeded in a 48-well plate were transfected with the DNA mixture composed of the same molecular ratio of pG5luc, GAL4p300, and VP16pCAF, VP16Sp1N, or VP16Sp1C. 30 ng of pRL-TK and a different amount of pGEM-ZF(+) were used as internal control and carrier DNA, respectively. The total amount of DNA is 0.3 μg/well. Every point was triplicate, and the data are representative of three experiments. +, present; –, absent.
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