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Advances in Brief

CREB-binding Protein and p300/CBP-associated Factor Are Transcriptional Coactivators of the p53 Tumor Suppressor Protein[1]

Daniel M. Scolnick,[2] Nabil H. Chehab,[2] Elena S. Stavridi, Marcus C. Lien, Loretta Caruso, Elizabeth Moran, Shelley L. Berger, and Thanos D. Halazonetis[3]

Department of Molecular Genetics, The Wistar Institute [D. M. S., N. H. C., E. S. S., M. C. L., L. C., S. L. B., T. D. H.], Programs in Biochemistry [D. M. S., N. H. C.] and Neuroscience [M. C. L.], and Department of Pathology and Laboratory Medicine [T. D. H.], University of Pennsylvania, Philadelphia, Pennsylvania 19104, and Fels Institute for Cancer Research and Molecular Biology, Temple University School of Medicine, Philadelphia, Pennsylvania 19140 [E. M.]

Abstract

The structurally related transcriptional coactivators p300 and CBP possess histone acetyltransferase activity and associate with P/CAF, which is also a histone acetyltransferase. CBP and p300 have properties of tumor suppressor proteins; their interaction with P/CAF is disrupted by the adenoviral E1A oncoprotein, and the genes encoding CBP and p300 are mutated in human cancer. We observed a physical interaction between the transactivation domain of the p53 tumor suppressor protein and CBP. Furthermore, CBP and P/CAF enhanced the ability of p53 to activate expression of the endogenous *p21^cip1/waf1^* gene, whereas E1A and dominant negative CBP mutants suppressed p53-dependent *p21^cip1/waf1^* expression. These studies link two tumor suppressor families and provide a framework for understanding the molecular mechanism by which p53 activates transcription.

Introduction

Many sequence-specific transcription factors require coactivator/adaptor proteins to activate transcription (1). Recent evidence suggests that some coactivators act by modifying the chromatin structure (2). For example, the structurally related coactivators p300 and CBP and their partner P/CAF have intrinsic histone acetyltransferase activity (3–5).

The CBP and p300 coactivators have properties of tumor suppressors; they are targeted by the adenoviral-transforming protein E1A (6–8), and the genes encoding them are mutated in human cancer (9). This could imply that they function as coactivators of a transcription factor that is a tumor suppressor. One such factor is p53, a protein implicated in the development of more than one-half of all human tumors (10). In yeast, the transcriptional activity of ectopically expressed p53 is dependent on the Ada2-GCN5 adaptor complex (11). Because yeast Ada2 and GCN5 have sequence similarity to mammalian p300/CBP and P/CAF, respectively, we examined whether p300/CBP and P/CAF function as transcriptional coactivators of p53 in mammalian cells.

Materials and Methods

Recombinant Plasmids. Plasmids pSV2hp53BS (expressing human p53; Ref. 12), pRSV-CBP (murine CBP; Ref. 6), pCMV-p300 (human p300; Ref. 7), and pCX-Flag-P/CAF (P/CAF; Ref. 5) have been described previously.

Plasmid pGEM-CBP, which contains the entire coding sequence of murine CBP cloned in pGEM4 as a *Bam*HI fragment, was linearized with *Sst*I and *Xho*I and self-ligated to generate pGEM-CBP(1507–2441). Plasmid pGEMhp53wtN, a derivative of pGEMhp53wtB (12) with engineered *Nco*I, *Eag*I, and *Sal*I restriction sites at codons 1, 83, and right after the termination codon, respectively, was linearized with *Eag*I and *Sal*I and self-ligated to generate pGEMhp53wtN(1–83). The *Nco*I-*Hin*dIII p53 sequences in pGEMhp53wtN and pGEMhp53wtN(1–83) were cloned in pGEX4T1 (Pharmacia, Piscataway, NJ) for expression as GST fusions. Plasmids pGEX4T1CBP(1680–1915) and (1799–1915) were derived by cloning PCR fragments corresponding to CBP residues 1680–1915 and 1799–1915, respectively, into pGEX4T1.

Plasmids pSV2E1A12S and pSV2cdk2 contain E1A 12S and cdk2 cDNAs cloned in the pSV2 mammalian expression vector (12). Plasmids pCDNA3-HA-CBP(1430–2441), (1916–2441), and (1430–1916) express COOH-terminal fragments of CBP with a HA[4] tag fused to their NH_2 terminus. They were derived by introducing a HA tag between the *Hin*dIII and *Not*I sites of pcDNA3 (Invitrogen, Carlsbad, CA), then CBP COOH-terminal fragments digested with Bst1107 I-*Xba*I (residues 1430–2441), *Hpa*I-*Xba*I (residues 1916–2441), and Bst1107 I-*Hpa*I (residues 1430–1916) were cloned in pcDNA3-HA linearized with *Not*I and *Xba*I.

Binding of p53 to CBP. Glutathione Sepharose 4B beads (Pharmacia) were equilibrated in 1× IP buffer (2× IP: 50 mM HEPES, pH 7.4; 200 mM NaCl; 10 mM $MgCl_2$; 200 mM EDTA; 0.4 mg/ml BSA; and 0.2% Tween 20) and then were incubated with GST-hybrid proteins. The beads were then washed, incubated with ^{35}S-labeled *in vitro* translated proteins for 1 h at 4°C, and washed twice with 1× IP buffer and once with 2× IP buffer. ^{35}S-labeled proteins that bound to the beads were analyzed by SDS-PAGE and visualized by autoradiography.

For interaction *in vivo*, MCF-7 cells were irradiated (9 gray), and nuclear extracts were prepared 45 min later. p53 was immunoprecipitated with antibody PAb421 in 1× IPiv buffer (25 mM HEPES, pH 7.4; 50 mM NaCl; 5 mM $MgCl_2$; 100 mM EDTA; 0.2 mg/ml BSA; and 0.01% Tween 20). The beads were washed three times in 2× IPiv buffer, and coprecipitated p300/CBP was detected with antibody NM11 (Oncogene Research Products, Cambridge, MA).

p53 Transcriptional Activity. Saos-2 cells were transfected by calcium phosphate precipitation with plasmids expressing wild-type p53 (0.03 μg or 1 μg, as indicated), 1 μg CBP, 1 μg P/CAF, 1 μg cdk2N145, and/or 1 μg E1A as described (12). Forty-eight h after transfection, the cells were washed twice with PBS and lysed by scraping in 0.5 ml of 2× RIPA buffer (40 mM Tris, pH 7.4; 2 mM EDTA; 300 mM NaCl; 20 mM KCl; 2% NP40; 0.2% Triton-X-100; and 0.2% SDS). p53 and p21^cip1/waf1^ protein levels were monitored by Western blotting using monoclonal antibodies from Oncogene Research Products and Transduction Laboratories (Lexington, KY).

Tumor Suppression Assay. SK-NSH neuroblastoma cells were transfected in triplicate with 5 μg of plasmids expressing either human p53, human papillomavirus E6 (plasmid pCMVneo16E6), adenoviral E1A 12S or P/CAF and 1 μg of pSV7neo, a plasmid that confers neomycin resistance (12). G418-resistant colonies were counted 4 weeks later.

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[2] The first two authors contributed equally to this work.

[3] To whom requests for reprints should be addressed, at the Wistar Institute, 3601 Spruce Sreet, Philadelphia, PA 19104-4268. E-mail: halazonetis@wista.wistar.upenn.edu.

[4] The abbreviations used are: HA, hemagglutinin; Rb, retinobastoma; GST, glutathione *S*-transferase; CBP, CREB-binding protein; P/CAF, p300/CBP-associated factor; TAF, TATA-binding protein-associated factor.

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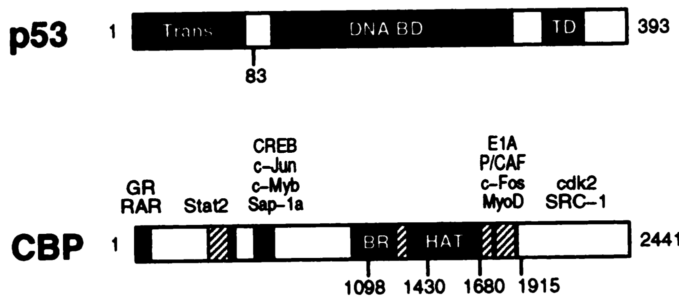

Fig. 1. Schematic diagrams of p53 and CBP proteins. In *p53*, the three highly conserved functional domains are indicated by ■. *Trans*, transactivation domain; *DNA BD*, sequence-specific DNA-binding domain; *TD*, tetramerization domain. In *CBP*, regions of CBP with over 75% amino acid identity to p300 are filled. Structural elements within these regions of high similarity include a bromo-domain (*BR*), a histone acetyltransferase domain (*HAT*), and putative Zn-finger domains (▨). The binding sites for transcription factors that bind to CBP or p300 are indicated: *GR*, glucocorticoid receptor; *RAR*, retinoic acid receptor; *CREB*, cyclic-AMP response element-binding protein; *SRC-1*, steroid receptor coactivator-1.

Results

Three major functional domains are recognized in p53: an NH_2-terminal transactivation domain (residues 1–80), a central sequence-specific DNA binding domain (residues 94–293), and a COOH-terminal tetramerization domain (residues 325–355; Ref. 10). To determine whether p53 and CBP associate *in vitro*, a full-length p53 protein fused to GST was incubated with *in vitro* translated fragments of murine CBP (Fig. 1 shows schematic diagrams of full-length p53 and CBP). NH_2-terminal CBP fragments, exemplified by CBP (1–1098), failed to bind to GST-p53, whereas a COOH-terminal CBP fragment encompassing residues 1507–2441 was captured by GST-p53. The interaction was dependent on the presence of the p53 transactivation domain: GST-p53Δ3–79, which lacks p53 residues 3–79, failed to interact with CBP (Fig. 2*A*). GST fused to the NH_2-terminal 83 amino acids of p53 also captured CBP (Fig. 2*B*).

The p53 transactivation domain contains two contiguous subdomains extending between residues 1–39 and 40–78, respectively (11). These subdomains function synergistically, and each contains two adjacent hydrophobic residues (Leu^{22}-Trp^{23} and Trp^{53}-Phe^{54}) that are critical for activity. Both subdomains were required for the interaction between p53 and CBP. Deletion of residues 1–39 or 34–78 or substitutions targeting Leu^{22} and Trp^{23} or Trp^{53} and Phe^{54} abolished binding of CBP to full-length p53 (Fig. 2*B*). These deletions and substitutions also abolished the interaction of full-length p53 with CBP (data not shown).

To map more finely the p53 binding site on CBP, we fused GST to CBP residues 1680–1915 or 1799–1915. Full-length *in vitro* translated p53 was captured by the former protein but not by the latter (Fig. 2*C*). These results map the p53 binding site to a cysteine-rich region of CBP with high homology to p300. The p53 binding site is close to the P/CAF binding site on CBP; however, the two binding sites are distinct because P/CAF binds to a GST hybrid protein fused to residues 1800–1880 of CBP (5).

To determine whether p53 and CBP interact *in vivo*, we examined MCF-7 breast carcinoma cells, which express wild-type p53 and which respond to irradiation by inducing the expression of p53-dependent genes (13). Nuclear extracts prepared from irradiated MCF-7 cells were immunoprecipitated with antibody PAb421, which recognizes the COOH terminus of p53, or with a control antibody. Immunoblotting revealed coprecipitated p300/CBP specifically in the p53 immunoprecipitates (Fig. 2*D*).

The physical interaction between p53 and CBP suggested that CBP may function as a transcriptional coactivator for p53. To examine this hypothesis, Saos-2 osteosarcoma cells, which lack endogenous p53 (12), were transiently transfected with plasmids directing the expression of p53 and the CBP and P/CAF coactivators. In addition, some experiments included a plasmid-directing expression of cdk2N145, a dominant negative cdk2 mutant, that enhances the coactivator function of CBP (14). The transcriptional activity of p53 was monitored by assaying the expression of the endogenous $p21^{cip1/waf1}$ gene, a known p53-responsive gene (15).

A small amount (0.03 μg) of transfected plasmid expressing p53 did not lead to the detectable expression of $p21^{cip1/waf1}$ protein on Western blots. The expression of CBP, p300, or P/CAF on their own had no significant effect on the ability of p53 to induce $p21^{cip1/waf1}$. However, CBP, P/CAF, and cdk2N145 together enhanced the ability of p53 to induce $p21^{cip1/waf1}$ expression (Fig. 3, *A* and *B*). We note that

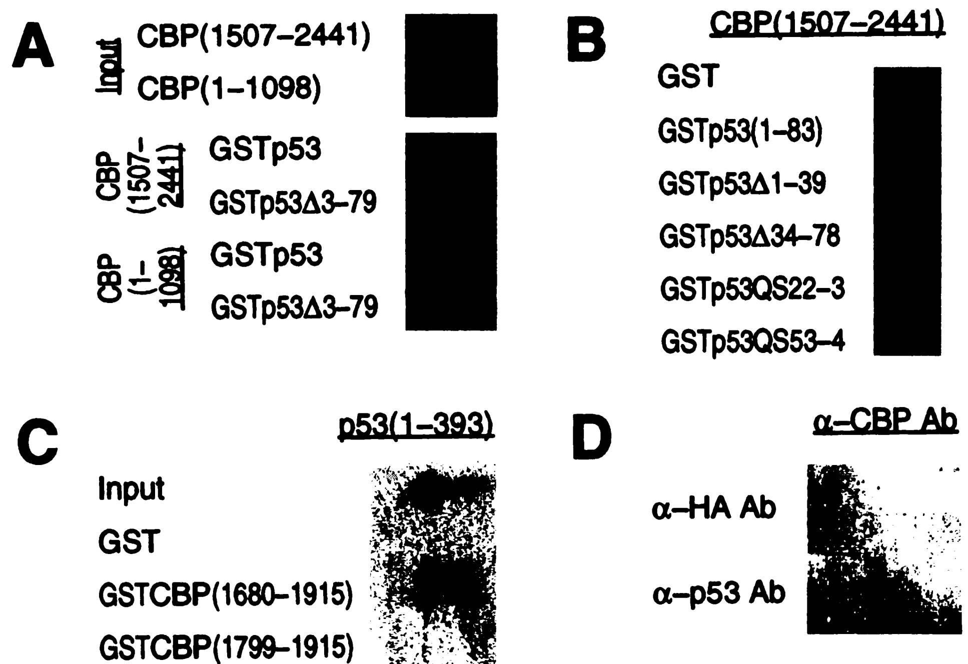

Fig. 2. Physical interaction between p53 and CBP. *A-C*, interaction *in vitro*; GST was fused to full-length p53 (*A*) or to its NH_2-terminal 83 residues (*B*) and assayed for its ability to capture *in vitro*-translated CBP proteins. In *C*, GST was fused to CBP peptides and assayed for its ability to capture *in vitro*-translated full-length p53. p53 mutants contain either deletions (Δ) of the indicated residues or amino acid substitutions: mutant QS22–3 introduces Gln at position 22 and Ser at position 23; mutant QS53–4 introduces Gln at position 53 and Ser at position 54. CBP proteins are named by the residues included in the constructs. *D*, interaction *in vivo*; MCF-7 nuclear extracts were immunoprecipitated with antibodies (*Ab*) that recognize p53 (PAb421) or the hemagglutinin (*HA*) tag (12CA5), as a control. Coprecipitated CBP was detected with the antibody NM11.

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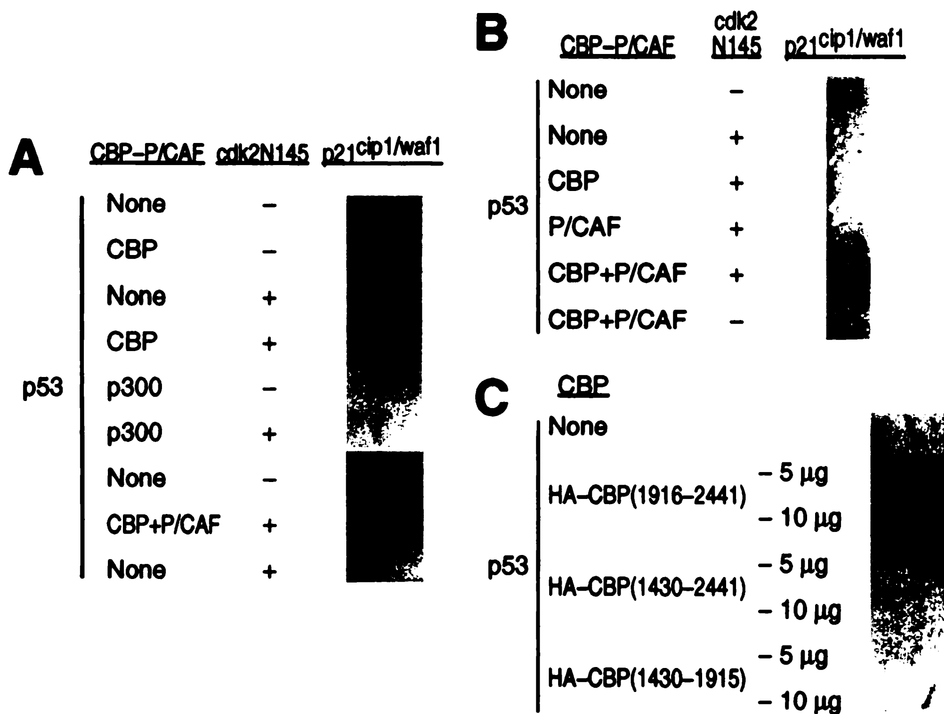

Fig. 3. Regulation of p53 transactivation by CBP and P/CAF. In *A* and *B*, CBP and P/CAF in the presence of a dominant negative cdk2 mutant (cdk2N145) enhance the ability of p53 to induce expression of endogenous $p21^{cip1/waf1}$. *C*, suppression of p53-dependent induction of $p21^{cip1/waf1}$ by dominant negative CBP mutants corresponding to residues 1430–2441 and 1430–1915 but not by CBP(1916–2441), which is not a dominant negative mutant.

the magnitude of induction with this experimental system is limited by transfection efficiency and that the effects of CBP and P/CAF in this and all subsequent experiments could not be attributed to changes in p53 expression because p53 protein levels were monitored by Western blotting and remained constant (data not shown).

To further explore whether CBP and P/CAF are physiologically relevant coactivators of p53, we examined whether dominant negative CBP mutants suppress p53-dependent transcription. Previous studies have shown that a truncated p300 protein extending between residues 1514–1922 has dominant negative activity (16). This protein retains the P/CAF binding region, but lacks histone acetyltransferase activity. We generated essentially equivalent CBP mutants that extend between residues 1430–1915 and 1430–2441. Both these mutants suppressed the expression of $p21^{cip1/waf1}$ induced by transfecting 1 µg of plasmid-directing p53 expression. In contrast, a CBP protein encompassing residues 1916 to 2441, which lacks the p53 and P/CAF binding sites, did not suppress $p21^{cip1/waf1}$ expression (Fig. 3*C*).

Like dominant negative CBP mutants, the adenoviral E1A protein also inhibits p300/CBP function; E1A competitively inhibits binding of P/CAF to CBP and p300 (5). We anticipated that E1A would inhibit p53-dependent transcription of $p21^{cip1/waf1}$, because wild-type E1A suppresses the transcriptional activity of p53 from reporter plasmids (17–19). Indeed, an E1A mutant protein, E1AG126, that binds to CBP but not to Rb, inhibited the p53-dependent expression of the endogenous $p21^{cip1/waf1}$ gene. Inhibition was relieved by the coexpression of CBP and P/CAF (Fig. 4*A*). In further support of a role of the CBP-P/CAF complex on p53 transactivation, E1AΔ2–36, a mutant that binds to Rb but not to CBP, did not inhibit the induction of $p21^{cip1/waf1}$ expression by p53.

E1A also inhibited the tumor suppressor activity of p53. SK-NSH neuroblastoma cells express endogenous wild-type p53, which restricts their ability to form colonies in tissue culture; genes that inhibit the function of endogenous p53, such as dominant negative p53 mutants and the human papillomavirus E6 gene, lead to enhanced colony formation. In this study, E1A 12S also enhanced colony formation (Fig. 4*B*). This correlated with p300/CBP binding activity;

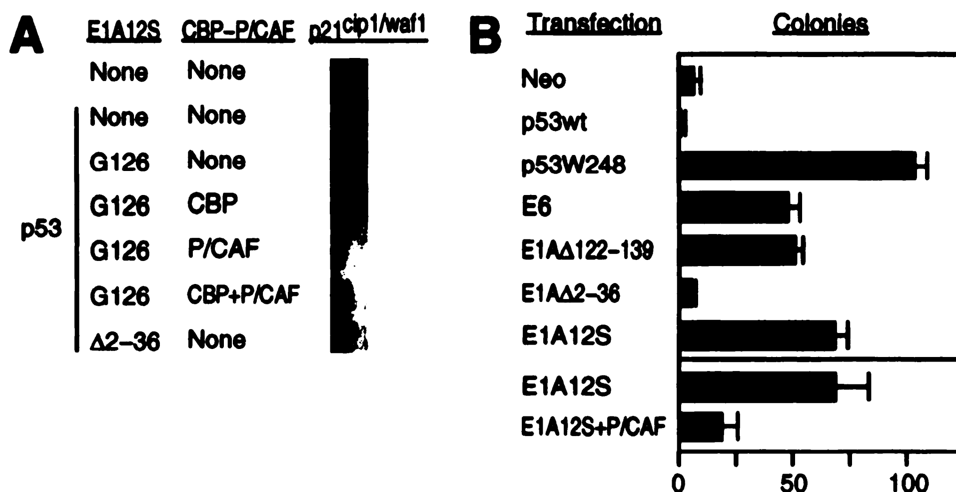

Fig. 4. P/CAF rescues E1A-induced inhibition of the transcriptional and tumor suppressor activities of p53. *A*, transcriptional activity; inhibition of p53 transactivation by an E1A mutant that binds CBP and rescue by CBP and P/CAF. *B*, tumor suppressor activity; SK-NSH neuroblastoma cells, whose ability to form colonies is suppressed by endogenous wild-type p53, were stimulated to form colonies with an E1A mutant that binds to CBP. This activity of E1A was antagonized by P/CAF. The E1A12S mutants with a single amino substitution of Glu^{126} to Gly (*G126*) or with the deletion of residues 122–139 do not bind Rb, whereas the mutant with a deletion of residues 2–36 (Δ2–36) does not bind CBP or p300.

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E1AΔ122–139, which binds to p300/CBP but not to Rb, also enhanced colony formation, whereas E1AΔ2–36, which binds to Rb but not to p300/CBP, did not enhance colony formation. The coexpression of P/CAF with E1A led to a more than 3-fold reduction in the colony-forming activity of E1A, consistent with competition between E1A and P/CAF for binding to CBP (Fig. 4*B*).

Discussion

The function of p300 and CBP as transcriptional coactivators of p53 explains why mutations of the *p300* and *CBP* genes have been associated with human malignancy (9) and why the full transforming activity of E1A requires its NH_2 terminus, which mediates binding of E1A to p300/CBP (20). Furthermore, the observation that P/CAF also facilitates the transcriptional activity of p53 anticipates the discovery of mutations within the *P/CAF* gene in human tumors.

In addition to CBP, the human TATA-binding protein-associated factors TAFII31 and TAFII70 and their drosophila counterparts also bind to the transactivation domain of p53 (21, 22). Their interaction with p53 involves residues Leu^{22} and Trp^{23}, the same residues that are required for the binding of p53 to CBP. If p53 binds CBP and TAFs in a mutually exclusive manner, then p53 might activate transcription in two steps. The first step would involve the recruitment of CBP and P/CAF, leading to histone acetylation and the weakening of the interaction of chromosomal DNA with histones (2). In the second step, p53 contacts TAFs rather than CBP. Recruitment of TAFs could be facilitated by the weak interaction between histones and DNA because several TAFs, including TAFII31, have structural homology to histones H3 and H4 and may displace the histone core from DNA (23). Both steps would be inhibited by the Mdm2 proto-oncoprotein, the binding site of which on p53 overlaps the CBP and TAF binding sites (24).

The COOH terminus of p300/CBP physically interacts with cdk2/cyclin E, and the ability of p300/CBP to function as a coactivator of NF-κB is enhanced by cdk2N145, a dominant negative cdk2 mutant (14). Cdk2N145 also enhanced the ability of CBP to support p53-dependent transcription. These results may provide an explanation for the cell cycle-regulated activity of p53. p53 induces cell cycle arrest in G_1 of the cell cycle, when cdk2 activity is low, but not in S, when cdk2 activity is high (25). It is tempting to propose that CBP imparts cell cycle-regulated activity to p53 by modulating its ability to activate transcription. Finally, we note that since this study was published, three other groups have also reported that CBP functions as a coactivator for p53, although they did not investigate the role of P/CAF (26–28).

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