The transcriptional co-activator proteins p300 and CBP stimulate adenovirus E1A conserved region 1 transactivation independent of a direct interaction

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Abstract p300 and CBP are two related transcriptional co-activator proteins required by many cellular transcription factors for activity. The adenovirus E1A protein binds p300 and CBP through its amino-terminus and conserved region (CR) 1. Fusing CR1 to a heterologous DNA-binding domain creates a potent transcriptional activator, suggesting that CR1 might activate transcription by recruiting p300/CBP to the promoter. We show that both p300 and CBP enhances CR1-dependent transactivation. However, this enhancement occurs independently of a direct interaction with E1A and does not correlate with the CR1 activator function.

Key words: p300; CBP; Transcription activation; Adenovirus E1A

1. Introduction

The adenovirus E1A proteins transactivate the adenovirus early promoters, induce S-phase in the host cell and immortalize rodent cells. These activities are mediated by cellular proteins associating with the E1A proteins. Three conserved regions (CR1, 2 and 3) and the extreme N-terminus of the protein are involved in binding multiple cellular proteins (reviewed in [1]). Activation of transcription in HeLa cells is mainly mediated by the E1A CR3 domain which interacts with a number of transcription factors, allowing E1A, which by itself does not bind DNA, to associate with the promoter region [2]. In contrast, in primary cells, efficient transactivation of the adenovirus early promoters require both the CR1 and the CR3 domains [3,4]. This result suggests that factors associating to the CR1 domain play an important role in E1A transactivation during the natural virus life cycle. Interestingly, the CR1 domain has an intrinsic transactivation capacity. Thus, fusing CR1 to a heterologous DNA-binding domain creates a transcriptional activator which is as potent as the CR3 domain [5–7].

The CR1 domain has been shown to be of critical importance for a lytic adenovirus infection by forcing infected cells to enter the S-phase. This appears to be accomplished in two ways. First, the CR1 and CR2 domains of E1A bind the Retinoblastoma protein and its relatives p107 and p130. This results in a release of the E2F family of transcription factors, which are needed to activate genes required for DNA synthesis, from inhibitory complexes with the Retinoblastoma family of proteins (reviewed in [8]). In the second pathway, E1A prevents host cell differentiation by repressing transcription of differentiation specific genes. This is accomplished by binding of the highly related transcriptional co-activator proteins p300 [9] and CREB-binding protein (CBP) [10] to the E1A N-terminus and the CR1 domain [11–14].

Recent data show that many unrelated transcription factors require the p300/CBP co-activator proteins for activity (reviewed in [15]). Interestingly, p300/CBP associate with the histone acetyltransferase p/CAF [16] and in addition posses intrinsic histone acetylase activity [17,18]. Collectively, available data suggest that p300/CBP may activate transcription by inducing chromatin remodelling. In our earlier work we showed that mutations eliminating E1A binding of the Retinoblastoma family of proteins did not affect the CR1 transactivation function, whereas a mutation that would be predicted to affect p300/CBP binding resulted in crippling of the activator function. This finding raised the possibility that CR1 functions as a transactivator by recruiting the p300/CBP co-activator proteins to the promoter. Here we show that both p300 and CBP stimulate CR1-dependent transactivation. However, by using mutants of E1A and p300 we also show that this stimulation is independent of an interaction with E1A. Thus, we conclude that neither CBP nor p300 is the critical co-activator protein required for the E1A CR1 transactivation function.

2. Materials and methods

2.1. DNA constructs

Most Gal4 fusion plasmids have previously been described [5,19] as have the CAT reporter constructs [20]. All Gal4 fusion proteins encode the DNA-binding domain [amino acids (aa) 1–147] of Gal4 fused to different parts of E1A. The nomenclature used to name plasmids are as follows; Met, R, and C indicate that the junction between the Gal4 region and E1A sequence are at the E1A initiation codon (Met), the *Rsa*I site at nucleotide 636 (R) or the *Cla*I site at position 917 (C). Boff and Doff indicate that a translational stop codon was introduced after the *Bsp*EI (position 825) or *Dde*I (position 1241) restriction sites, respectively. Gal-MetBoffΔCR1 was constructed by transfer of the ΔCR1 mutation from pML005ΔCR1 [5] to Gal4-MetBoff. Gal-Raa75 and Gal-Raa60 are PCR variants of Gal-RBoff that introduce stop codons after aa 75 and aa 60 of E1A, respectively. PCR clones were verified by sequencing. Gal-Raa68 was constructed by ligating the *Eco*RI-blunt ended *Ava*I fragment of Gal-RBoff into *Eco*RI-blunt ended *Xba*I of Gal-R12SXoff.

Plasmids expressing Glutathione S-transferase (GST) fusion proteins were constructed by transfer of the E1A part of Gal4 fusion plasmids into either the pGEX-1λT or pGEX-2T vectors (Pharmacia). Plasmids pRc/CMV-mCBP-HA [10] (here designated plasmid CBP), CMVβ-p300-CHA and CMVβ-p300del30 [9] (here designated plasmids p300 and p300del30) express CBP and p300 proteins with an HA epitope tag fused to the C-terminus. The CMV promoter backbone plasmid has been described (designated pSCT in [21]).

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2.2. Transfection and reporter gene analysis

Subconfluent HeLa monolayer cells were grown and transfected by the calcium phosphate coprecipitation technique as previously described [5]. When necessary, transfections were supplemented with either pUC 19 or salmon sperm DNA up to a total of 12–15 μg of DNA per 60 mm dish. Three μg of CAT reporter plasmid was transfected with 0.2 μg of Gal-E1A fusion plasmids and 1 or 5 μg of empty CMV vector, or p300 or CBP expressing plasmids. CAT extracts were prepared by freeze-thawing [5]. Different amounts of extract were assayed to allow accurate quantitation of strong activators. All experiments were performed at least three times. Data were quantitated by phosphorimager analysis using a Molecular Dynamics or BioRad machine.

2.3. GST-binding assay

GST fusion proteins were expressed in *E. coli* and purified on glutathione-Sepharose as described in the Pharmacia manual. Similar amounts of GST fusion proteins were incubated with 8 μl in vitro translated ^{35}S labelled CBP or the C-terminus of p300 in 400 μl of NTN buffer (20 mM Tris pH 7.5, 100 mM NaCl and 0.5% NP40) for one hour at 4°C. The beads were washed three times with the same buffer, bound proteins eluted with loading buffer and resolved on 7.5% SDS-PAGE gels. pRc/CMV-mCBP-HA was used for in vitro transcription/translation of CBP. An oligonucleotide containing a T7 RNA polymerase promoter, an ATG translation initiation codon and sequence complementary to p300 beginning at aa 1613 (5′-ATTAATACGACTCACTATAGGCACCATGGTTGATCCTGATCCTC-3′) together with an oligo complementary to the HA epitope (5′-TATCTATCCGAGGGAGGCGTAGTC-3′) was used to amplify the C-terminus of p300 by PCR. Coupled in vitro transcription/translation was performed in a wheat germ extract (Promega). We were unable to generate full-length in vitro translated CBP, the product migrates at approximately 180 kDa. The C-terminus of p300 migrates with a somewhat larger size than expected (approximately 95 kDa instead of 86 kDa).

3. Results

3.1. E1A CR1 transactivation, but not CR3 activation, is stimulated by p300 and CBP expression

We have shown that fusion of the first 90 amino acids (aa) of E1A, including CR1, to the DNA-binding domain of the yeast transcription factor Gal4, results in an activator at least as potent as the previously described Gal-CR3 fusion protein [5]. We also showed that mutation of E1A aa 66–68 dramatically reduced transactivation. This mutation is expected to eliminate p300/CBP binding to E1A [3] and we therefore tested the involvement of these proteins in transcription activation by the CR1 domain. HeLa cells were transfected with Gal-MetBoff (E1A aa 1–90) and the G1E1BCAT reporter containing a single Gal4 DNA-binding site, in the absence or presence of p300 or CBP. As shown in Fig. 1, co-transfection of either p300 or CBP stimulated CR1 transactivation in a dose-dependent manner. The amount of CR1 activator in this and the following experiments was titrated to give only minimal activation, thereby allowing the visualization of the effects of p300 and CBP. Interestingly, Gal-CR3 activation (Gal-CDoff) was largely unaffected by p300 or CBP co-transfection (Fig. 1). The small effect seen on Gal-CR3 activation was similar to the effect of p300/CBP on the reporter alone. However, p300 and CBP co-transfection stimulated transcription by the unrelated activators Gal-VP16 (Fig. 1) and Gal-c-jun (not shown). Thus, although p300 and CBP will stimulate transcription of a number of activation domains, the effect on E1A transactivation is specific to the CR1 activator.

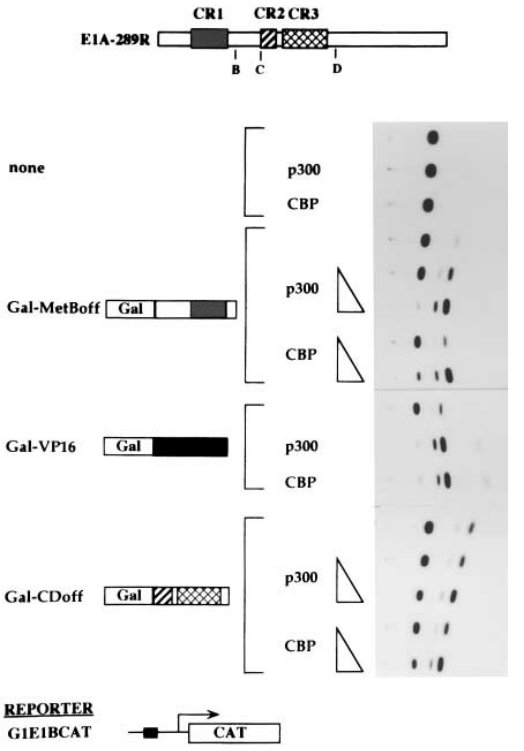

Fig. 1. p300 and CBP stimulate Gal-E1A CR1 transactivation in a dose-dependent manner. Gal-MetBoff (expressing aa 1–90 of E1A, including CR1), Gal-VP16 and Gal-CDoff (aa 121–192 of E1A, including CR3) were transfected with the G1E1BCAT reporter plasmid in the absence or presence of increasing amounts of plasmids p300 or CBP. Shown is a schematic representation of the E1A-289R protein (top) as well as the Gal4 fusion proteins (left) and a representative CAT assay to the right.

3.2. Transactivation defective mutants of E1A are stimulated by p300 expression

In the context of the wild type (wt) E1A protein the N-terminus is critical for binding of p300/CBP [12]. However, removal of the first 27 aa creates a transactivation domain, Gal-RBoff (E1A aa 28–90), that is even more potent than Gal-MetBoff ([5]; see also Fig. 5A). This protein was stimulated to a similar extent as Gal-MetBoff by p300 or CBP co-transfection (see below). Interestingly, the substitution mutant Gal-RBoff sub66–68 which has lost almost all of its transactivation function was still stimulated by p300 co-transfection (Fig. 2). Thus, the transactivation capacity of the Gal-E1A fusion proteins does not correlate with p300 stimulation. This conclusion is consistent with the effect of p300 expression on C-terminally truncated variants of Gal-RBoff (Fig. 2). These truncated proteins progressively lose their transactivation capacity as assayed on the G5E1BCAT reporter. However, as shown in Fig. 2, Gal-Raa75 (E1A aa 28–75) and Gal-Raa68 (E1A aa 28–68) were stimulated by p300 expression to a similar extent as Gal-RBoff. In contrast, Gal-Raa60 (E1A aa 28–60) was not stimulated by p300 co-transfection. This is not because p300 stimulation requires a functional CR1 activation domain, since mutating aa 66–68 (Gal-RBoff sub66–68) eliminated transactivation but still allowed for p300 stimulation (Fig. 2). Similar results were obtained for CBP (not shown). Taken together, these results suggest that stimulation by p300 or CBP does not correlate with the CR1 transactiva-

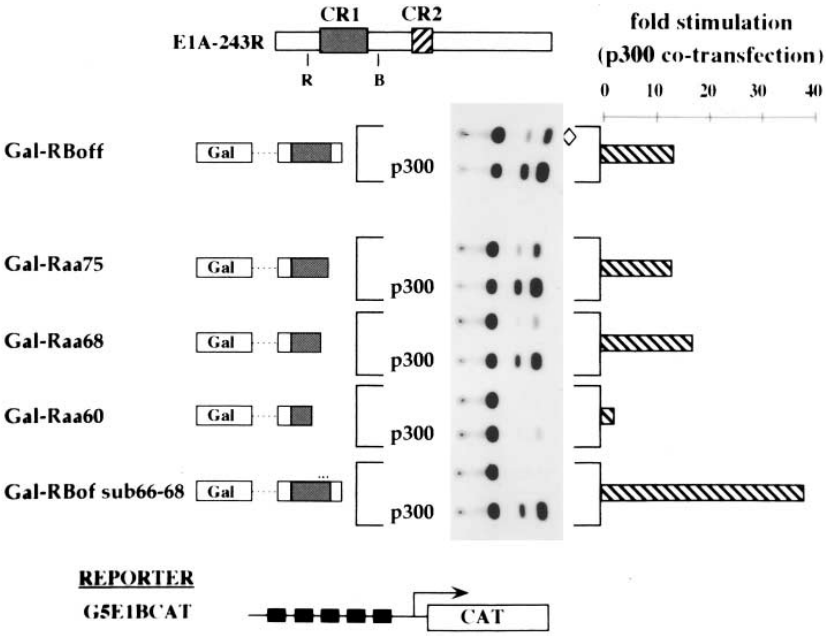

Fig. 2. Stimulation of transcription by p300 does not correlate with the transactivation capacity of CR1. Gal-RBoff (E1A aa 28–90) and mutants thereof were co-transfected with the G5E1BCAT reporter plasmid in the absence or presence of p300 plasmid. A schematic representation of the E1A-243R protein (top) and the Gal4 fusion proteins (left), a representative CAT assay and a quantitation thereof is shown. Note that the quantitative result is given as fold stimulation caused by p300 co-transfection and not the relative activity of each mutant protein. ◇, Since Gal-RBoff is a very potent transactivator protein only 5 μl of extract was assayed, while 150 μl extract of the other mutants was assayed.

tion function. The results further suggest that aa 60–66 are critical for p300 stimulation.

The results presented this far indicate that residues critical for the interaction between E1A and p300/CBP in the E1A wt context are not required for p300/CBP stimulation of Gal-E1A transcription. Thus, p300 and CBP enhancement of Gal-E1A transcription appears to be independent of an interaction with E1A. To further test this hypothesis, we determined whether the p300 mutant protein p300del30 which is unable to interact with E1A [9] stimulates Gal-E1A transcription. As shown in Fig. 3, p300del30 co-transfection stimulates Gal-MetBoff and its derivatives to a similar extent as wt p300. Taken together, these results suggest that p300 stimulates Gal-E1A transcription-independent of a direct interaction with the E1A protein.

The data shown in Fig. 2 indicate that CR1, in the absence of the N-terminus, is sufficient for p300 stimulation. To test whether CR1 is required for p300 stimulation, we compared the effect of p300 co-transfection on Gal-R12SE/P- (E1A aa 28–142) and Gal-R12SE/P-ΔCR1 (removing aa 38–65) transactivation. As shown in Fig. 4, deletion of both CR1 and the N-terminus (Gal-R12SE/P-ΔCR1) eliminated transactivation as well as p300 stimulation. Interestingly, the N-terminus (Gal-MetBoffΔCR1), although unable to activate transcription by itself, was stimulated by p300 co-transfection (Fig. 4). Collectively these results show that the E1A N-terminus

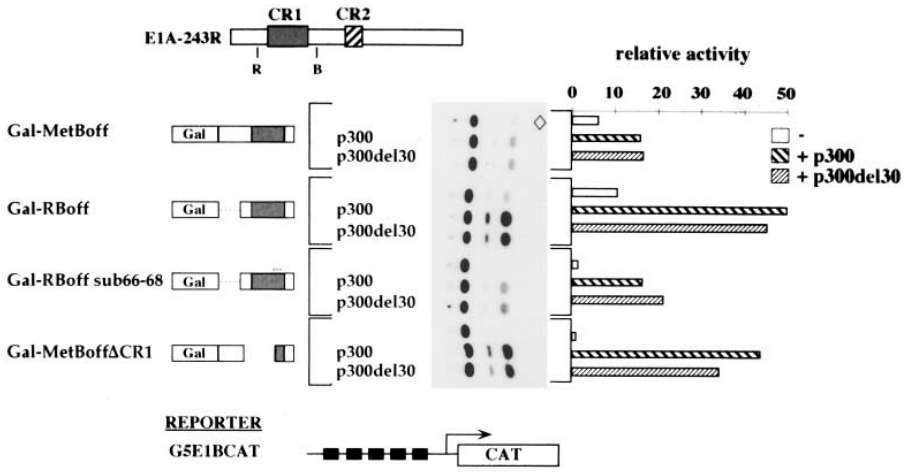

Fig. 3. A p300 mutant protein (p300del30) unable to bind to E1A stimulates Gal-E1A transcription. Gal-MetBoff and mutants thereof were tested for stimulation by p300 or p300del30 co-transfection. Shown is a schematic picture of the E1A-243R protein (top) and the Gal4 fusion proteins (left) together with a representative CAT assay and a quantitation to the right. ◇, Gal-RBoff is a potent transactivator protein and was therefore assayed on the G1E1BCAT reporter while the other Gal4 fusion proteins were assayed on G5E1BCAT.

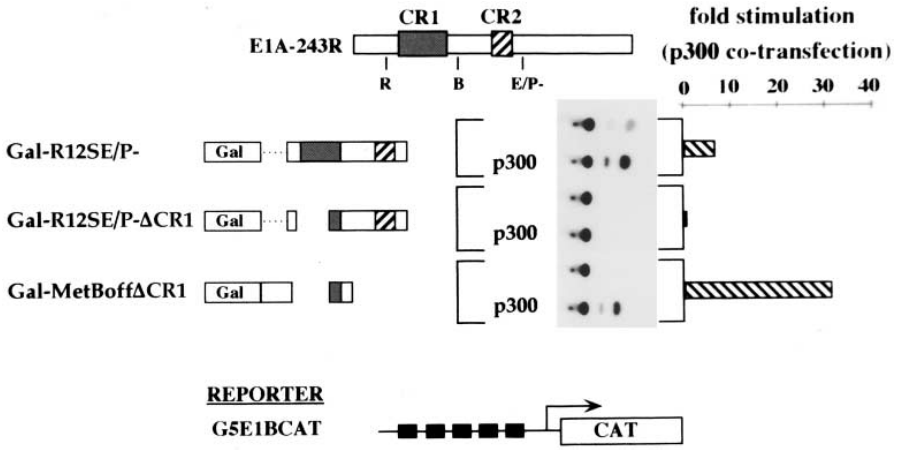

Fig. 4. The E1A N-terminus and CR1 are independently able to mediate p300 stimulation of transcription. Gal-R12SE/P- (E1A aa 28–142), Gal-R12SE/P-ΔCR1 (deleting aa 38–65) and Gal-MetBoffΔCR1 (E1A aa 1–90 with a deletion of aa 38–65) were transfected with the G5E1B-CAT reporter plasmid in the absence or presence of p300 plasmid. Shown is the E1A-243R protein (top), the Gal4 fusion proteins (left) and a CAT assay with a quantitation to the right. Note that the quantitative result is given as fold stimulation caused by p300 co-transfection and not the relative activity of each mutant protein.

and CR1 independently of each other are able to mediate p300 stimulation.

3.3. CBP and p300 stimulation of transcription differ in their E1A sequence requirement

Both p300 and CBP co-transfection stimulated Gal-MetBoff (E1A aa 1–90) transactivation (Fig. 5B). Removing the N-terminus as in Gal-RBoff or mutating aa 66–68 (Gal-RBoff sub66–68) did not distinguish between p300 and CBP enhancement of transcription. For both p300 and CBP, CR1 is thus sufficient for stimulation and the stimulation does not require a functional CR1 activation domain (Fig. 5A). Interestingly, Gal-MetBoffΔCR1 which was efficiently stimulated by p300 expression (Figs. 4 and 5B) was not stimulated by CBP (Fig. 5B). Thus, the E1A N-terminus or CR1 independently of each other mediate p300 stimulation. In contrast, CBP stimulation requires the CR1 domain. Most importantly, neither CBP nor p300 enhancement of transcription correlates with the CR1 transactivation function since both stimulate Gal-RBoff sub66–68 (Fig. 5B).

3.4. In vitro binding of p300 or CBP to E1A does not correlate with the CR1 transactivation function

To obtain additional proof that p300 or CBP interaction with E1A does not correlate with the activity of the CR1 transactivator we performed in vitro protein-protein interaction studies. For these experiments in vitro translated p300 and CBP proteins were tested for their binding capacity to GST-E1A fusion proteins expressed in *E. coli* (Fig. 6). Notably, in vitro translation of both p300 and CBP yielded multiple truncated protein products. This difficulty in translating full length p300 and CBP proteins have previously been noted by others [22]. In vitro translated CBP did not interact with GST but efficiently bound to GST-MetBoff and somewhat less efficiently to GST-MetBoffΔCR1. CBP failed to interact with GST-RBoff and GST-RBoff sub66–68. The binding data of

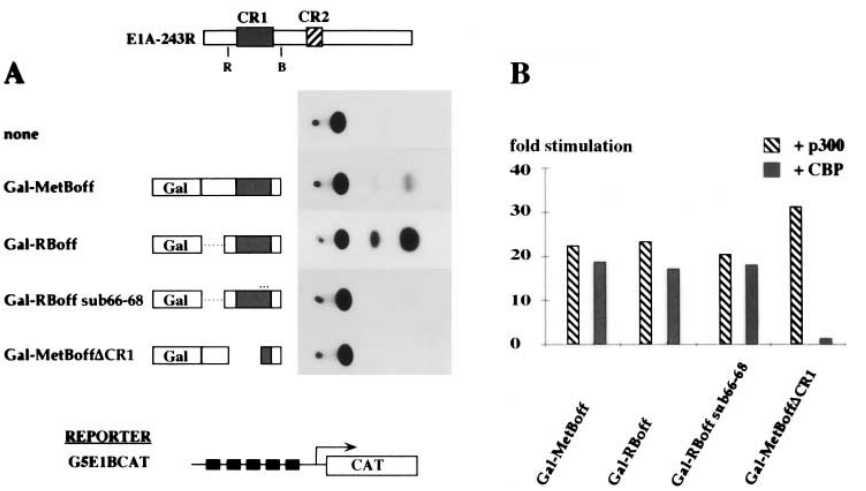

Fig. 5. Both p300 and CBP enhance CR1 transactivation but only p300 stimulates the E1A N-terminus. (A) Representation of the E1A-243R protein (top) and the Gal4 fusion proteins (left). A CAT assay comparing the activating properties of Gal-MetBoff mutants in the absence of p300/CBP expression is shown to the right. (B) Quantitation of the stimulatory effects of p300 or CBP co-transfection. Note that the quantitative result is given as fold stimulation caused by p300 or CBP co-transfection and not the relative activity of each mutant protein.

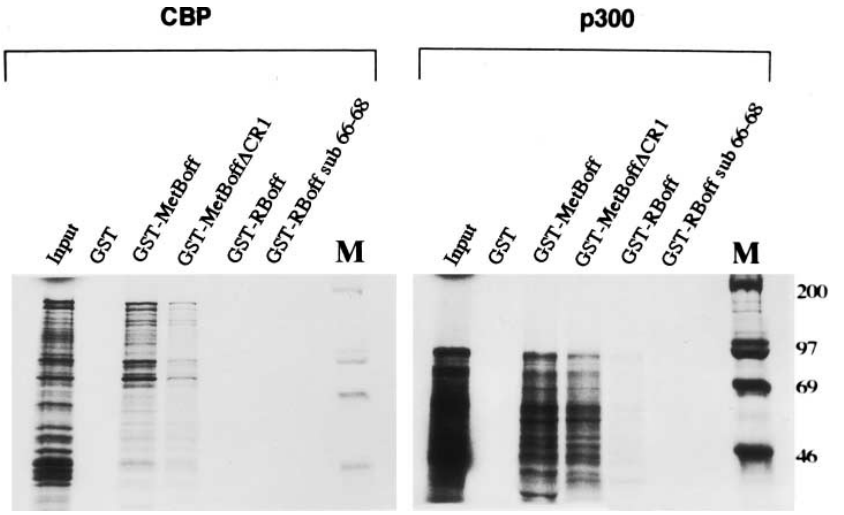

Fig. 6. Binding of CBP or p300 to E1A in vitro does not correlate with the transcription stimulatory effect. In vitro translated CBP or p300 was tested for binding to bacterially produced GST-E1A fusion proteins. Input represents 25% of the material used in the binding reactions. M indicates a protein size marker.

CBP to the MetBoff mutant proteins therefore are completely opposite to its effect on transcription. Thus, MetBoffΔCR1 is not stimulated by CBP in co-transfection experiments but binds CBP, while RBoff and RBoff sub66–68 are stimulated by CBP but do not bind CBP.

In vitro translated p300 efficiently bound GST-MetBoff but failed to interact with GST. Binding to GST-MetBoffΔCR1 was somewhat reduced while binding to GST-RBoff was severely reduced and no interaction with GST-RBoff sub66–68 could be detected. Although p300 is able to efficiently stimulate transcription by all of these proteins, it only weakly interacts with RBoff and fails to interact with RBoff sub66–68. In conclusion, these in vitro binding studies corroborate our conclusion that p300 and CBP stimulation of CR1 transactivation does not require a direct interaction with E1A. These data are consistent with our observation that the p300del30 protein that lacks the E1A interaction domain still stimulates Gal-CR1 transactivation.

4. Discussion

We have previously shown that fusing the first 90 aa of E1A to the Gal4 DNA-binding domain creates a very potent transcription activator protein, Gal-MetBoff [5]. This region of E1A interacts in the context of the wt protein with the transcriptional co-activator proteins p300 and CBP [1]. Based on functional and structural similarities between the E2F1 activation domain and the amino-terminal fragment of E1A (aa 1–90) it was recently proposed that E1A binding to CBP correlates with the CR1 activation function [23]. To test the hypothesis that CR1 functions as an activator by recruiting p300/CBP to the promoter we analyzed a number of mutants of Gal-MetBoff (aa 1–90) for their ability to be stimulated by p300 or CBP. In conclusion, our results show that E1A binding to p300 or CBP does not correlate with the CR1 activator function. Both p300 and CBP overexpression enhances transcription by Gal-CR1. However this enhancement of Gal-CR1 transcription appears to be independent of a direct interaction of p300/CBP with E1A. We show that some mutations that reduce or eliminate Gal-CR1 transactivation can be stimulated by p300/CBP co-transfection (Figs. 2 and 5). Thus, p300/CBP enhancement of transcription does not correlate with the CR1 transactivation function. Furthermore, the E1A N-terminus and the C-terminal part of CR1, including aa 66–68, which are important for the stable binding of p300/CBP to the E1A wt protein ([3,24] and data not shown), are not necessary for p300/CBP to enhance Gal-CR1 transcription. Also, a p300 mutant protein (p300del30) that does not bind E1A [9] stimulates Gal-MetBoff to a similar extent as the wt p300 protein (Fig. 3). Similar results were obtained for all Gal-CR1 mutants tested, including the ones unable to activate transcription.

Further evidence for p300 stimulation of Gal-CR1 transcription-independent of a direct E1A interaction was obtained by analyzing the in vitro binding characteristics of p300/CBP to GST-E1A fusion proteins. Most importantly, we observe that Gal-RBoff sub66–68 which has lost almost all of its activation capacity (Fig. 5), and fails to bind CBP or p300 in vitro (Fig. 6) was stimulated by both p300 and CBP co-transfection to the same extent as Gal-MetBoff (Fig. 5) which efficiently binds both p300 and CBP (Fig. 6). Thus, E1A binding to p300/CBP does not correlate with the CR1 trans activator function. Consistent with these results, we have previously failed to detect an interaction of Gal-E1A fusion proteins with p300/CBP in vivo [5]. Collectively, our results suggest that p300/CBP enhances transcription by E1A CR1 independent of a direct protein-protein interaction.

Interestingly, we found that the E1A sequence requirements for p300 and CBP stimulation differ. Two independent domains of E1A mediate p300 stimulation; the N-terminus (aa 1–27) and CR1 (aa 28–68) whereas CBP activation is more restricted requiring the E1A-CR1 domain. Thus, although p300 and CBP are highly related at the sequence level, their activities can be distinguished. Consistent with this notion, mutation of CBP has been implicated in the Rubinstein-Taybi syndrome [25], suggesting that p300 cannot compensate for CBP function in this disorder.

Although the p300/CBP stimulation of Gal-MetBoff transcription occurs independently of a direct interaction with E1A, the effect is not non-specific since Gal-CR3 transactiva-

tion is unaffected (Fig. 1). Thus p300/CBP overexpression is not causing a general activation of transcription by altering the chromatin structure by, for example, histone acetylation [15]. More likely, the E1A N-terminus and the CR1 domain interact with, at the present time, unknown cellular proteins that in turn recruit p300/CBP to the promoter with E1A. In this scenario, CR3 or its interacting proteins would not need p300/CBP recruitment for function. However, the physiological significance of such an indirect recruitment of p300/CBP to the E1A N-terminal fragment is questionable since Gal-MetBoffΔCR1 and Gal-RBoff sub66–68 by themselves do not function as activators (Fig. 5A).

So far it is not clear if the CR1 activator is required for lytic virus growth. It has been noted that activation of the adenovirus early promoters in primary cells require both the CR1 and CR3 domains [3,4]. The significance of the CR1 activator during virus-infection of primary cells has not been directly tested. However, available mutational studies do not suggest a direct link between the CR1 activator and E1A transactivation in non-transformed cells [3,4].

E1A binding of p300/CBP correlates with the ability of E1A to repress enhancer-dependent transcription (reviewed in [1]). The results presented here show that the classical E1A transcription repression function and the CR1 activation function are distinct biological activities. However, it should be noted that CR1 represses a skeletal-muscle-specific enhancer independently of Retinoblastoma protein or p300/CBP binding [26]. Thus, CR1 interacting proteins other than p300/CBP and the Retinoblastoma family of proteins contribute to the multiple functions of CR1.

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References

[1] Moran, E. (1994) Semin. Virol. 5, 327–340.
[2] Liu, F. and Green, M.R. (1994) Nature 368, 520–525.
[3] Wong, H.K. and Ziff, E.B. (1994) J. Virol. 68, 4910–4920.
[4] Wong, H.K. and Ziff, E.B. (1996) J. Virol. 70, 332–340.
[5] Bondesson, M., Mannervik, M., Akusjarvi, G. and Svensson, C. (1994) Nucleic Acids Res. 22, 3053–3060.
[6] Sollerbrant, K., Chinnadurai, G. and Svensson, C. (1996) Nucleic Acids Res. 24, 2578–2584.
[7] Lipinski, K.S., Kroner Lux, G., Esche, H. and Brockmann, D. (1997) J. Gen. Virol. 78, 413–421.
[8] Nevins, J.R. (1992) Science 258, 424–429.
[9] Eckner, R., Ewen, M.E., Newsome, D., Gerdes, M., Decaprio, J.A., Lawrence, J.B. and Livingston, D.M. (1994) Genes Dev. 8, 869–884.
[10] Chrivia, J.C., Kwok, R.P., Lamb, N., Hagiwara, M., Montminy, M.R. and Goodman, R.H. (1993) Nature 365, 855–859.
[11] Stein, R.W., Corrigan, M., Yaciuk, P., Whelan, J. and Moran, E. (1990) J. Virol. 64, 4421–4427.
[12] Wang, H.G.H., Rikitake, Y., Carter, M.C., Yaciuk, P., Abraham, S.E., Zerler, B. and Moran, E. (1993) J. Virol. 67, 476–488.
[13] Arany, Z., Newsome, D., Oldread, E., Livingston, D.M. and Eckner, R. (1995) Nature 374, 81–84.
[14] Lundblad, J.R., Kwok, R.P.S., Laurance, M.E., Harter, M.L. and Goodman, R.H. (1995) Nature 374, 85–88.
[15] Shikama, N., Lyon, J. and La Thangue, N.B. (1997) Trends Cell. Biol. 7, 230–236.
[16] Yang, X.J., Ogryzko, V.V., Nishikawa, J., Howard, B.H. and Nakatani, Y. (1996) Nature 382, 319–324.
[17] Bannister, A.J. and Kouzarides, T. (1996) Nature 384, 641–643.
[18] Ogryzko, V.V., Schiltz, R.L., Russanova, V., Howard, B.H. and Nakatani, Y. (1996) Cell 87, 953–959.
[19] Sadowski, I., Ma, J., Triezenberg, S. and Ptashne, M. (1988) Nature 335, 563–564.
[20] Lillie, J.W. and Green, M.R. (1989) Nature 338, 39–44.
[21] Öhman, K., Nordqvist, K. and Akusjarvi, G. (1993) Virology 194, 50–58.
[22] Eckner, R. et al. (1996) Mol. Cell. Biol. 16, 3454–3464.
[23] Trouche, D. and Kouzarides, T. (1996) Proc. Natl. Acad. Sci. USA 93, 1439–1442.
[24] Wang, H.G., Rikitake, Y., Carter, M.C., Yaciuk, P., Abraham, S.E., Zerler, B. and Moran, E. (1993) J. Virol. 67, 476–488.
[25] Petrij, F. et al. (1995) Nature 376, 348–351.
[26] Sandmöller, A., Meents, H. and Arnold, H.H. (1996) Mol. Cell. Biol. 16, 5846–5856.