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COMMENTARY

Cell Cycle Regulation of the Transcriptional Coactivators p300 and CREB Binding Protein

*Andrew W. Snowden and Neil D. Perkins**

DEPARTMENT OF BIOCHEMISTRY, UNIVERSITY OF DUNDEE, DUNDEE DD1 4HN, SCOTLAND, U.K.

ABSTRACT. To respond to changes in its environment, the cell utilizes mechanisms that integrate extracellular signals with specific changes in gene expression. To better understand these critical regulatory mechanisms, research has focused, for the most part, on the identification of sequence-specific DNA-binding proteins, such as the nuclear factor κB (NF-κB) or activator protein 1 (AP-1) families of transcription factors, that interact with the promoter and enhancer elements of genes induced or repressed during cellular activation. More recently, however, it has become apparent that non-DNA-binding transcriptional coactivators, such as p300 and CREB binding protein (CBP), previously thought to function primarily as "bridging" proteins between DNA-bound transcription factors and the basal transcription complex, play a critical regulatory role as integrators of diverse signalling pathways with the selective induction of gene expression. In this commentary, we shall discuss the implications of a particular aspect of this growing and expanding field: how cell cycle regulation of p300 and CBP impacts our understanding of cellular differentiation, the response to DNA damage, and oncogenesis. BIOCHEM PHARMACOL **55**;12:1947–1954, 1998. © 1998 Elsevier Science Inc.

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The initiation of transcription by promoter- or enhancer-bound DNA-binding proteins is dependent upon the recruitment of the basal transcription complex and RNA polymerase II [1, 2]. It has become apparent recently that, in addition to directly contacting components of the basal complex, such as TFIIB and TFIID, interaction with a class of non-DNA-binding proteins, termed coactivators, is critical for the efficient stimulation of transcription *in vivo*. Coactivators can function as a bridge between upstream DNA-binding proteins and the basal complex. In addition, however, they also appear to play a role in chromatin remodelling—the opening up of the nucleosome structure to allow efficient access of DNA-binding proteins and the basal complex to the promoter. Among these coactivators, p300, first identified as a protein interacting with the adenovirus E1A oncoprotein [3–5] and CBP†, initially identified as binding to the phosphorylated form of the cAMP-responsive transcription factor CREB (CREB Binding Protein) [6], have received much attention due to their promiscuous interactions with a wide range of inducible transcription factors. These include, in addition to CREB, MyoD [7–9], c- and v-Myb [10, 11], STAT 1 and 2 [12–14], E2F [15], p53 [16–18], nuclear hormone receptors [19–22], AP-1 [23, 24], YY1 [25], and NF-κB [26, 27].

p300 and CBP are highly homologous, containing many common structural motifs (Fig. 1) and, to a great extent, functionally overlap [4, 5, 28–30]. Similar to other transcriptional activators, analysis of p300/CBP function has revealed multiple interactions with general transcription factors. CBP has been shown to complex directly with the RNA polymerase II holoenzyme as a result of an interaction with RNA helicase A [31, 32]. p300/CBP also interact with TFIIB [33] and TBP, a component of TFIID [34, 35]. Interestingly, p300 and CBP have also been shown to be HATs [36, 37] and, furthermore, to associate with multiple other HATs such as P/CAF [38] and members of the SRC family of nuclear hormone receptor coactivators [19, 39–41]. Nucleosomes are potent repressors of transcription *in vitro* and *in vivo*, and acetylation of the amino terminal tails of nucleosomal histones by HATs is thought to destabilize histone–DNA interactions and facilitate access and binding of DNA-binding proteins [42, 43]. In this manner, HATs are postulated to assist transcriptional activation by modulating nucleosomal repression of specific promoters. Acetyl transferases may also influence transcription by other mechanisms, however. Recent studies show that p300/CBP can also acetylate p53, resulting in stimulation of its DNA-binding activity [44]. Furthermore, p300/CBP will acetylate the general transcription factors TFIIE and TFIIF [45], although the functional significance of these latter observations remains to be determined.

* Corresponding author: Dr. Neil D. Perkins, Department of Biochemistry, University of Dundee, Wellcome Trust Building, Dundee DD1 4HN, Scotland, U.K. Tel. 44-1382-345606; FAX 44-1382-322558; E-mail: nperkins@bad.dundee.ac.uk.

† *Abbreviations:* AML, acute myeloid leukemia; AP-1, activator protein 1; bHLH, basic helix-loop-helix; CBP, CREB binding protein; Cdk, cyclin-dependent kinase; CKI, cyclin-dependent kinase inhibitor; FGF, fibroblast growth factor; HAT, histone acetyl transferase; MAP, mitogen-activated protein; NF-κB, nuclear factor κB; NGF, nerve growth factor; PDGF, platelet-derived growth factor; PKA, protein kinase A; Rb, retinoblastoma; TBP, TATA binding protein; and TGFβ, transforming growth factor beta.

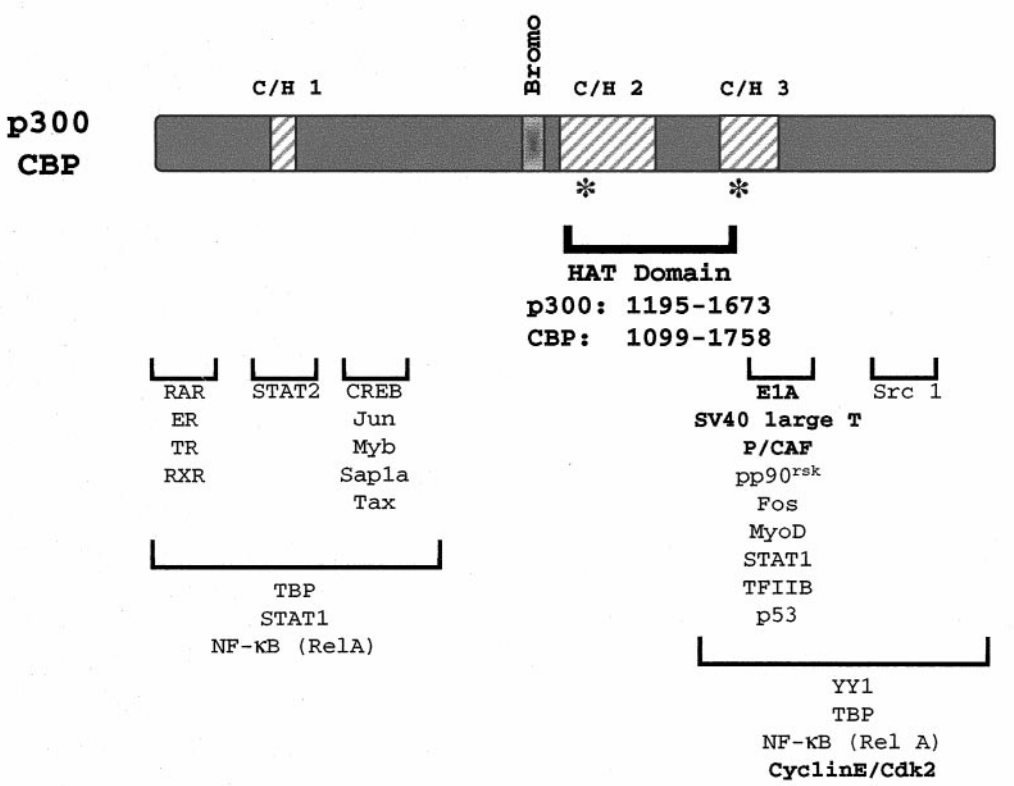

FIG. 1. Schematic diagram of p300/CBP. For simplicity, p300 and CBP are shown together as a composite diagram. A more detailed description of the areas of homology between these proteins can be found in Glass *et al.* [30] and Shikama *et al.* [29]. p300 and CBP are 2414 and 2440 amino acids long, respectively. The positions of the bromodomain (Bromo), the histone acetyl transferase (HAT) domain, and the cysteine/histidine (C/H) rich domains are indicated. The locations of the mutations in p300 associated with colorectal and gastric carcinomas are indicated with asterisks. The approximate binding sites for other transcription factors and coactivators are indicated. A more detailed description of these binding sites can be found in Shikama *et al.* [29].

From these studies it is apparent that p300/CBP coactivation could occur through multiple pathways:

- by assisting in the recruitment of the RNA polymerase II to promoters through interaction directly with polymerase II holoenzyme and general transcription factors.
- through the acetylation of nucleosomes, either directly or through the recruitment of additional HAT proteins, enabling access of DNA-binding proteins to the promoter.
- through the acetylation of transcription factors themselves.

p300 and CBP are not passive adaptor proteins, however, but are themselves critical regulatory proteins whose activity is modulated by multiple signal transduction pathways. The cAMP-activated kinase PKA phosphorylates CBP, stimulating its ability to facilitate the induction of transcription by CREB [6, 46]. The MAP kinase pathway also potentiates coactivation by p300/CBP [46], and MAP kinase has been shown to phosphorylate CBP *in vitro* [47] and *in vivo* [46]. Furthermore, growth factors, such as NGF or insulin, which signal through the Ras-MAPK pathway, activate the S6 kinase, $pp90^{rsk}$, which can subsequently bind directly to p300/CBP [48]. The binding of $pp90^{rsk}$ to p300/CBP was required for the differentiation of PC12 cells into neurons and also resulted in the inhibition of CREB/cAMP-mediated transcription. Interestingly, the kinase activity of $pp90^{rsk}$ did not appear to be required, suggesting that these effects were mediated by protein:protein interactions rather than protein phosphorylation. The precise mechanism through which these signalling pathways influence p300/CBP function, whether it be regulation of HAT activity or association with other coactivators or general transcription factors, is unclear at present.

These observations demonstrated that p300 and CBP directly participate in the decision-making processes of the cell. These are not the only mechanisms through which p300/CBP function results in crosstalk between divergent signalling pathways since, relative to the concentration of DNA-binding transcription factors, p300 and CBP are present at limiting levels within the nucleus. This can result in the sequestration of p300/CBP by certain DNA-binding proteins, suppressing the ability of other transcription factors to induce gene expression. While the full significance of this has yet to be realized, it is clear that this transcriptional regulatory mechanism has great potential to influence the function of transcription factors whose activity is dependent on their ability to recruit p300/CBP to the promoters and enhancers of the genes that they regulate. For example, recent studies show that STAT proteins, p53,

and nuclear hormone receptors, such as the estrogen or thyroid hormone receptors, inhibit AP-1 transcriptional activation in a p300/CBP-dependent manner [13, 16, 19].

p300/CBP AND CELL CYCLE REGULATION OF GENE EXPRESSION

Progression through the eukaryotic cell cycle is controlled by the regulated expression of specific Cdk complexes. Conversely, the induction of CKIs that bind directly to Cdks or cyclin/Cdk complexes provides a mechanism to regulate their activity. Together, these proteins regulate the cellular decision to proliferate, differentiate, or arrest the cell cycle [49–52]. A direct link between p300/CBP and the cell cycle was first implied by a study demonstrating phosphorylation of p300 that initiated at S phase and continued through G_2 phase [53]. p300 has been shown to be an *in vitro* substrate for cyclin/Cdc2 and cyclin/Cdk2 complexes, with this phosphorylation being blocked by the addition of E1A [54]. More recently, a direct functional link between the cell cycle and regulation of p300/CBP has been established. This study demonstrated that transcriptional activation by the RelA(p65) subunit of NF-κB was strongly stimulated by cotransfection of the CKI p21 (WAF1/CIP1) but not by an unrelated CKI, $p16^{INK4A}$ [26]. This effect correlated with the inhibition, by p21, of the activity of a cyclin/Cdk complex associated with p300/CBP that coimmunoprecipitated with RelA. This cyclin/Cdk complex, which appeared to be predominantly cyclinE/Cdk2 although some Cdc2-containing complexes could also be detected, bound the carboxy terminal region of p300 (Fig. 1). Importantly, p21 enhanced the ability of p300 to function as a coactivator for RelA-dependent stimulation of transcription. Furthermore, the ability of a Gal4 fusion of full-length p300 or CBP to stimulate transcription is strongly enhanced by the cotransfection of p21 (Snowden A and Perkins N, unpublished observation). These results suggest that, during the cell cycle, p300 is negatively regulated by cyclinE/Cdk2, although the mechanism through which this is accomplished has not been established. It is intriguing that p300 appears to be predominantly associated with cyclinE/Cdk2, the cyclin/Cdk combination that regulates the G_1/S phase transition checkpoint. Cell cycle progression through G_1 requires the integration of external signals such as mitogens, growth factors, and the extracellular matrix with internal cellular signals regarding cell state, viability, and resources. It is possible that binding of cyclinE/Cdk2 to p300/CBP is required for entry into S phase and that mechanistically this might be related to the ability of E1A to similarly induce exit from G_1. Confirmation of this hypothesis will require reagents capable of blocking cyclinE/Cdk2 binding to p300/CBP without otherwise interfering with their catalytic activity.

The implications of these observations for our understanding of NF-κB function are numerous. Many factors can induce both NF-κB activity and p21 expression, including mitogens such as phorbol esters and serum growth factors, oxidative stress, and okadaic acid [55–58]. Differentiation of HL-60 cells into monocytes is also associated with the induction of p21 and requires the activation of NF-κB [59, 60]. Furthermore, DNA damage following treatment with UV light or ionizing radiation activates NF-κB [61, 62], which coincides with the induction of p21 by the tumour suppressor p53 (see below) [63, 64]. These observations suggest that p21 can functionally assist NF-κB transactivation of stress-responsive genes by alleviating cyclin-Cdk repression of p300/CBP.

p53, p21, p300/CBP AND THE RESPONSE TO DNA DAMAGE

It is probable, however, that the functional consequences of this transcriptional regulatory mechanism go far beyond NF-κB. The transition from G_1 to S phase represents a key regulatory step in the cellular response to DNA damage. Cell cycle arrest prior to S phase in untransformed cells is required to allow DNA repair to occur before DNA replication commences, and a key regulatory step in this process has been shown to be the up-regulation of p21 expression by the p53 tumour suppressor [56, 64, 65]. Because induction of p21 expression by p53 is dependent upon p300/CBP [17, 18], whose activity, in turn, is enhanced by p21 expression [26], there is potentially a positive feedback loop. p53 could increase its own transactivation potential through the effect of p21 on p300/CBP function (Fig. 2). Whether p21 enhances the ability of p300/CBP to acetylate p53, thus enhancing its DNA-binding potential, is not currently known. It is noteworthy that NF-κB is also induced by ionizing radiation [61, 62], which results in DNA damage. Thus, p53 might indirectly stimulate the activity of NF-κB through the enhancement of p300/CBP transactivation by p21. Such a mechanism could provide a route through which, should the process of DNA repair fail, p53 enhances the ability of NF-κB, a critical regulator of antigen presentation and the response to stress and infection, to prime the cell for rejection by the immune system.

ROLES OF p300/CBP AND p21 IN CELLULAR DIFFERENTIATION

p21 expression can also be induced in a p53-independent manner during the process of cellular differentiation as well as by a variety of stimuli, including serum stimulation and mitogens such as PDGF, FGF, and TGFβ [55–59, 66–71]. p21 expression is critical to many cellular differentiation programs involving permanent cell cycle exit, and, during mouse embryogenesis, p21 mRNA is localized exclusively to differentiated, post-mitotic tissues such as cartilage and skeletal muscle [69]. Skeletal muscle differentiation is regulated by the MyoD family of bHLH transcription factors, which activate muscle-specific gene expression and induce permanent cell cycle arrest and differentiation [67,

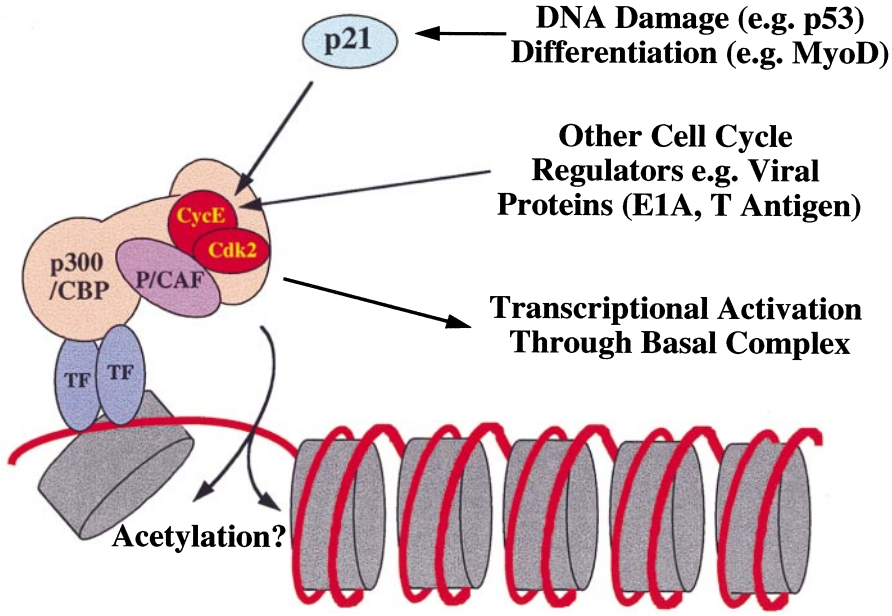

FIG. 2. Model of a cell cycle-regulated p300/CBP complex at a promoter. p300 and CBP are recruited by transcription factors (TF) such as NF-κB, p53, or MyoD to specific promoters where their activity can be regulated by cyclinE/Cdk2, p21, and viral oncoproteins.

69, 72–76]. Terminal cell cycle arrest in myogenic precursor cells is mediated by MyoD-dependent induction of p21 expression, which remains up-regulated in differentiated myotubes, while ectopic MyoD expression is capable of inducing cell cycle arrest in non-myogenic cells [67, 69]. For example, transfection of a MyoD expression plasmid into osteosarcoma (U2OS) cells induces cell cycle arrest, presumably via p21 induction, with subsequent cellular differentiation into a skeletal muscle phenotype [77]. p300/CBP have been shown to be essential for cell cycle arrest, terminal differentiation, and transcriptional activity of the myogenic bHLH proteins and are integral components of myogenic differentiation [7–9]. Thus, similar to the scenario depicted for p53 above, there is the potential for a positive feedback loop being established. In this case, MyoD, which requires p300/CBP for its transcriptional activity, induces p21, which, in turn, enhances the efficiency with which MyoD and p300/CBP induce their target genes (Fig. 2).

It is likely that this putative functional relationship between p300/CBP and p21 is also repeated with other transcription factor-regulated differentiation programs. p300/CBP are also utilized by myogenin, a bHLH transcription factor related to MyoD, which is also integral to myogenesis [8, 9], and the MEF2 family of transcription factors [9], which co-operate with bHLH proteins in muscle differentiation and reinforce myogenic gene expression and differentiation. The MEF2 transcription factors are also involved in the differentiation of cardiac and smooth muscle, underlying the potential general utilization of p300/CBP in multiple differentiation pathways. bHLH transcription factors are implicated in controlling differentiation in several other cell types. The bHLH transcription factor E47, which is involved in B-lymphocyte differentiation, interacts with and is coactivated by p300/CBP [9] and has been shown recently to induce p21 expression [78]. Melanocyte differentiation is dependent upon a bHLH transcription factor, Microphthalmia, which again interacts with and utilizes the p300/CBP coactivators [79]. As discussed earlier, NGF stimulation of cultured PC12 cells activates a Ras-MAPK pathway stimulating the induction of p21, causing subsequent G_1 arrest and neural differentiation [66], in a process dependent on the p300/CBP coactivators. Keratinocyte differentiation also involves p21 up-regulation and cell cycle arrest early in the differentiation program in a process requiring p300 [68].

Thus, it seems probable that the intimate functional association of p21 with p300/CBP will prove to be a critical component of the process of cellular differentiation. It is unlikely, however, that this is the only mechanism through which p300/CBP are regulated during this process, but whether such other processes work in cooperation with p21 or function independently will require further investigation.

p300/CBP AND TUMORIGENESIS

p300/CBP are utilized by transcription factors that regulate cell growth and proliferation, such as E2F, p53, AP1, and Myb [10, 11, 15–18, 24]. Together with their regulation by the cell cycle and the Ras/MAP signalling pathways, this suggests that p300 and CBP, analogous in many ways to the Rb transcriptional repressor, are a nexus for the integration of positive and negative proliferative signals. Furthermore, overexpression of either p300 or the p300/CBP associated factor P/CAF suppresses cell cycle progression *in vivo* [38]. It can be predicted, therefore, that p300 and CBP will prove to be intimately involved in the process of cellular transformation and the development of cancer.

Underpinning the putative role of p300/CBP as tumour suppressor genes are the reports that, similar to other proteins involved in the regulation of cell growth, they are

the targets of multiple viral oncoproteins. A critical aspect of viral transformation is the deregulation of cellular proliferation, essential for the completion of the viral life cycle, and viral oncoproteins, such as adenovirus E1A, the SV40 large T antigen, and HTLV-1 Tax, all target, interact with, and subvert p300/CBP function [80–84]. E1A and T antigen interact with the same carboxy terminal region of p300/CBP, and binding of E1A blocks the association of the p300/CBP-associated histone acetyltransferase P/CAF [38]. E1A is a potent stimulator of cellular proliferation and can inhibit the induction of p21 and consequently interfere with the differentiation of certain cell types, including myoblasts [7, 9], keratinocytes [68], and NGF-stimulated PC12 cells [66] through its interaction with p300/CBP. Furthermore, E1A-mediated suppression of the transcriptional activities of c-myb [10, 11], c-fos [23], CREB [80], Stat 1α [12], p53 [17, 18, 81], and MyoD [7, 8] can be overcome by overexpression of p300 or CBP. SV40 large T antigen is also capable of inhibiting various promoters in what seems to be an analogous manner to E1A [82, 83] and may inhibit p53 transactivation via its interaction with p300/CBP–p53 complexes [82]. Unlike E1A and T antigen, the HTLV-1 protein Tax utilizes p300 and CBP by mediating their interaction with unphosphorylated CREB, which then stimulates the transcription of HTLV genes in the absence of cAMP stimulation [84]. It is likely that future studies will uncover more viral proteins that target and subvert p300 and CBP.

There are other lines of evidence, in addition to being the target of viral oncoproteins, which implicate that the disruption of p300/CBP function contributes strongly towards cellular transformation. Point mutations in and around the HAT domain of p300 have been found in certain gastric and colorectal carcinomas, with associated loss of the other p300 allele [85]. In addition, a translocation resulting in the fusion of MOZ, a putative chromatin-associated DNA-binding factor with homology to acetyltransferases, in-frame with the amino terminal of CBP at codon 266, has been identified in AML [86]. Interestingly, another common translocation involving MOZ maps to the chromosome region containing p300, suggesting that oncogenic p300 translocations also occur [86]. A second CBP translocation associated with AML, fusing CBP to MLL, has been identified. MLL, a putative methyltransferase and silencing factor, is fused in-frame to CBP and, like MOZ, is fused to CBP at codon 266 in some patients, suggesting that CBP is susceptible to translocations within this area [87, 88]. How these mutations and translocations contribute towards tumorigenesis has yet to be determined; however, fusion of an active acetyltransferase to a silencing factor or chromatin-associated protein could broadly disregulate and disrupt transcriptionally inactive chromatin, a potentially oncogenic event.

How the role of p300 and CBP as tumour suppressors is linked to their interaction with cyclin/Cdk complexes is unclear at present. It is tempting to speculate that binding of cyclinE/Cdk2 to p300/CBP is required for the initiation of S phase and that regulation of this step, for example through the induction of p21, is critical for normal cell growth. In cells where induction of p21 is disrupted, such as through mutation of p53 or the expression of viral oncogenes, this cell cycle regulatory checkpoint would not function, and cellular proliferation would proceed unchecked. Of course, the presence of functionally redundant regulatory mechanisms within the cell make it unlikely that this process in isolation would lead to tumorigenesis, and p300/CBP could be expected to cooperate with other tumour suppressors, such as Rb, to oppose unchecked cellular proliferation.

CONCLUSION

In this article, we have discussed cell cycle regulation of p300/CBP function and speculated on the implications of this for our understanding of a number of important biological questions. We have focused on the role p21 might play in these p300/CBP-dependent processes. It is probable, however, that many of the issues we have raised can be applied to other CKIs such as p27 and p57 [49–52, 89]. Clearly, not all CKIs will function through p300/CBP. p16, for example, does not enhance the ability of NF-κB to stimulate transcription [26], presumably because p16 is incapable of interacting with Cdk2- or Cdc2-containing complexes [52]. Cell cycle regulation of p300/CBP must be integrated with the other signalling pathways that modulate their function. It is likely that a hierarchy of such signalling pathways exists. For example, $pp90^{rsk}$ binding to p300/CBP overrides signalling through PKA [48]. It is possible that the binding of cyclinE/Cdk2 to p300/CBP is only of functional importance in the absence of stimuli such as elevated levels of cAMP or growth factors such as NGF. For example, in some circumstances cAMP-activated CREB can block cellular proliferation [90], although in this case a role for p300/CBP has yet to be demonstrated. Alternatively, p300 and CBP might exist within a number of distinct complexes within the nucleus, responsive to different signalling pathways, that are selectively targeted to specific subsets of transcription factors and promoters dependent upon cellular context.

The explosion of interest in p300 and CBP over the last 2 years has resulted from their central importance to divergent areas of research. p300 and CBP integrate signalling with transcriptional regulation and gene expression with chromatin structure, and the promiscuous nature of their interactions has resulted in laboratories previously working on apparently distinct problems identifying a common set of interests. The complexity surrounding p300 and CBP has only started to be unravelled, however. It is likely that additional variants and homologues of p300/CBP exist [18, 35], and their functions will need to be determined. The relative contributions of interactions with the basal transcription complex versus HAT activity, as well as the targets of this acetylation, require further investigation. In addition, it is probable that the p300/CBP

family will emerge as targets for further signalling pathways. It is clear that an appreciation of how coactivators such as p300 and CBP function is critical for our understanding of the central role regulated and inducible gene expression plays in cell growth, differentiation, and disease.

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