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CBP and p300: HATs for different occasions

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Abstract

The transcriptional coactivators CREB binding protein (CBP) and p300 are key regulators of RNA polymerase II-mediated transcription. Genetic alterations in the genes encoding these regulatory proteins and their functional inactivation have been linked to human disease. Findings in patients, knockout mice and cell-based studies indicate that the ability of these multidomain proteins to acetylate histones and other proteins is critical for many biological processes. Furthermore, despite their high degree of homology, accumulating evidence indicates that CBP and p300 are not completely redundant but also have unique roles in vivo. Recent studies suggest that these functional differences could be due to differential association with other proteins or differences in substrate specificity between these acetyltransferases. Inactivation of the acetyltransferase function of either CBP or p300 in various experimental systems will no doubt teach us more about the specific biological roles of these proteins. Given the wide range of human diseases in which CBP and/or p300 have been implicated, understanding the mechanisms that regulate their activity in vivo could help to develop novel approaches for the development of therapeutic strategies.

Keywords: CREB binding protein (CBP); p300; Histone acetyltransferase; Specificity; Disease

1. Chromatin and acetylation

Regulation of transcription is a central mechanism by which cells respond to developmental and environmental cues. RNA polymerase II-mediated transcription in eukaryotes is to a large extent regulated at the level of chromatin, which forms a physical barrier for the binding of proteins to the promoter region of a target gene. The basic unit of chromatin is the nucleosome, which consists of an octamer of histone proteins around which the DNA is wrapped (see Fig. 1). The nucleosomes form an array that is ordered into higher-order chromatin structures. The two major enzymatic activities which make the DNA more accessible for the transcription machinery are the ATP-dependent remodelling complexes and HATs [1,2]. The prime targets of the HATs in chromatin are the N-terminal tails of the core histones H2A, H2B, H3 and H4, which protrude away from the DNA. Acetylation of these tails results in neutralization of the positively charged lysines, thereby modifying DNA–histone and histone–histone contacts [2,3]. The N-terminal histone tails are also subject to other modifications, like methylation [4], phosphorylation [5] and sumoylation [6]. Furthermore, the C-terminus of H2A and H2B can be ubiquitinylated [7]. These modifications not only change accessibility to the DNA and create specific docking sites for proteins [8], but they also represent the so-called ''histone code'', a bar code which may be involved in the establishment of epigenetic inheritance [9]. The discovery that several known transcriptional coactivator proteins contain HAT activity, while repressors possess histone deacetylase (HDAC) activity, has strongly linked histone acetylation to transcriptional activation, and deacetylation to repression [3,10].

When a specific gene is activated, a cascade of chromatin modifications mediated by the ATP-dependent remodelling complexes and HATs makes the DNA accessible for transcription factors, including general transcription factors such as TFIID. Following assembly of the correct combination of these proteins RNA polymerase II is recruited and transcription takes place. Interestingly, the combination of the chromatin modifying enzymes

Abbreviations: CBP, CREB binding protein; CREB, cAMP response element binding protein; FAT, factor acetyltransferase; HAT, histone acetyltransferase; MLL, mixed lineage leukaemia protein; MORF, MOZ related factor; MOZ, monocytic leukaemia zinc-finger protein; PHD, plant homeodomain; RTS, Rubinstein–Taybi syndrome

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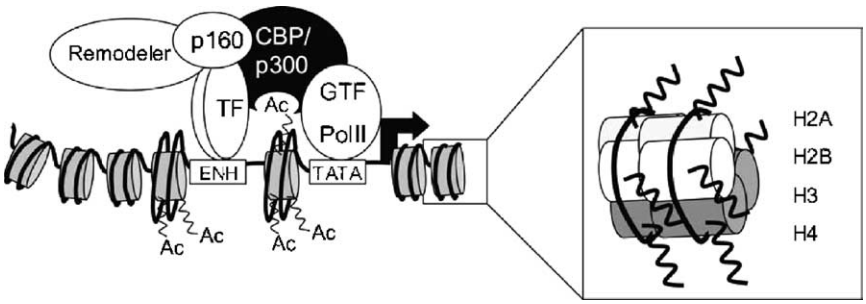

Fig. 1. Transcription regulation. Schematic representation of the promoter region of a gene, with the DNA wrapped around nucleosomes, which consist of octamers the histone proteins H2A, H2B, H3 and H4. A transcription factor dimer (TF), bound to the enhancer region (ENH), recruits remodeling factors (remodeler) and HATs, like CBP or p300 (CBP/p300), sometimes indirectly through other coactivators like the p160 proteins. CBP and p300 can make the DNA more accessible for other regulatory proteins by acetylating the histone tails (Ac). In addition, CBP and p300 can form a physical bridge between transcription factors and the general transcription factors (GTF) and RNA polymerase II (Pol II). See text for details.

required, and their order of recruitment, are promoter-specific, but at least one HAT is involved in activation of all the promoters presently studied in detail [11–15], indicating the fundamental importance of this protein family in biology.

2. Structure and function of the CBP and p300 proteins

The family of mammalian HATs includes CBP and its paralogue p300. CBP and/or p300 homologues are present in many multicellular organisms, including flies, worms and plants, but not in lower eukaryotes such as yeast [16–18]. CBP and p300 are ubiquitously expressed during mouse development [19]. Comparison of the amino acid sequences of these multidomain proteins from different species revealed the presence of numerous regions of near identity, including three cysteine–histidine rich regions (CH1, -2 and -3), the binding site for the CREB transcription factor, referred to as the KIX domain, the bromodomain, the HAT domain and the steroid receptor coactivator-1 interaction domain (SID), while other regions are poorly conserved [16] (see also Fig. 2). CBP and p300 can interact with the basal transcription factors TATA-binding protein (TBP [20]) and TFIIB [20,21] and/or form a complex with RNA polymerase II [22–25]. These interactions occur through an N- and C-terminal activation domain (See Fig. 1). In addition, CBP and p300 can bind to a variety of diverse transcription factors, and other proteins, through their CH-1, CH-3, KIX and SID domains [26,27]. By interacting simultaneously with the basal transcription machinery and with one or more upstream transcription factors, CBP and p300 function as physical bridges or scaffolds and thereby stabilize the transcription complex. Interestingly, several of these protein–protein interactions can be regulated by the same post-translational modifications that chromatin is subject to, such as phosphorylation [28–30], sumoylation [31] methylation [32,33], indicating that CBP and p300 are themselves targets of signalling cascades.

The second important aspect of the coactivator function of CBP and p300 is their ability to acetylate promoter proximal nucleosomal histones, resulting in increased accessibility of the DNA for other essential regulators [34–36]. Within the HAT domain of CBP and p300 two functionally important regions have been identified. One of these regions (amino acids 1459–1541 in CBP) is partly conserved between HAT proteins [37–40], and was postulated to be the coenzyme A (CoA) binding site [37,40]. The second important region in the HAT domain of CBP, which is not found in other HAT proteins, is the PHD type zinc-finger [41], also named leukaemia-associated-protein (LAP) finger [42] or trithorax consensus (TTC) finger [43].

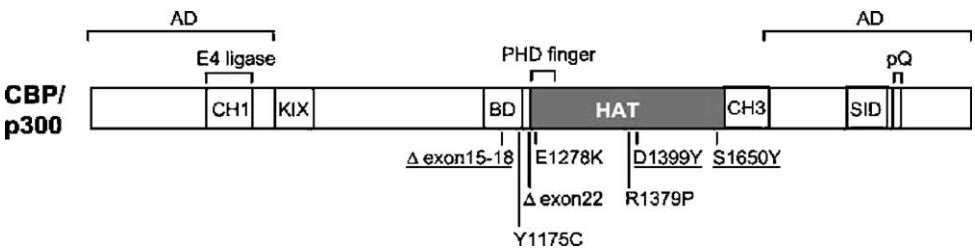

Fig. 2. Structure of the CBP/p300 protein family. Linear representation of the CBP/p300 proteins with regions and functional domains that are highly conserved between species indicated. Shown are the three cysteine–histidine rich regions (CH-1, -2 and -3), the E4 ligase domain, the KIX domain, the bromodomain (BD), the HAT domain and the p160 binding site, the N- and C-terminal activation domains (AD) and the polyglutamine stretch (pQ; unique to CBP). Also indicated are RTS-associated mutations in CBP and p300 mutations found in epithelial tumour cells (underlined). Please note that the Δ exon 22 mutation in CBP was also found in an epithelial cell line. See text for details.

This type of zinc-finger is characterised by a cysteine 4-histidine–cysteine 3 motif, and is predominantly found in proteins that function at the chromatin level [41]. The PHD finger is an integral part of the enzymatic core of the CBP acetyltransferase domain [44,45] but is dispensable for p300 HAT activity [44]. The HAT domain is preceded by the bromodomain, a 110 amino acid domain which is found in many chromatin-associated-proteins [8,46]. Bromodomains function as acetyl-lysine binding domains [47,48], and could therefore play a role in tethering CBP and p300 to specific chromosomal sites [49]. Interestingly, the bromodomain of p300 was recently shown to cooperate with the PHD finger in binding of hyperacetylated nucleosomes [50].

The preferred in vitro sites of acetylation on the N-terminal histone tails are lysine 12 (K12) and K15 in histone H2B, K14 and K18 in histone H3 and K5 and K8 in histone H4 [51]. In addition to their ability to acetylate histones, CBP and p300 have also been shown to acetylate other proteins like transcription factors and coactivators, and are therefore also called factor acetyltransferases (FAT [52,53]). Acetylation of non-histone substrates can result in either positive or negative effects on transcription by affecting, for example, protein–protein interactions (e.g. the activator of thyroid and retinoid receptors ACTR [54]), protein–DNA interactions (e.g. the high mobility group protein HMGI(Y) [55]), nuclear retention (e.g. the hepatocyte nuclear factor HNF4 [56]) or protein half-life (e.g. E2F [57]). While CBP and p300 are essential coactivators for a variety of transcription factors, the relative importance of the bridge/scaffold, HAT and FAT functions varies [58–60].

Like transcription, DNA replication and DNA repair also require access to the DNA and CBP and p300 have been implicated in these processes as well. They interact with various replication and repair proteins, including proliferating cell nuclear antigen (PCNA [61]), Flap endonuclease 1 (Fen1 [62]), DNA polymerase β [63], thymine DNA glycosylase [64], with the latter three also serving as acetylation substrates. In addition, CBP and p300 also play a role in a number of other cellular processes that are not directly linked to chromatin. CBP and p300 associate with the complex formed between cyclin E and cyclin-dependent kinase 2 (cdk2) and thereby regulating proper progression of the cell cycle [28,65,66]. Secondly, CBP and p300 are involved in degradation of the p53 transcription factor, which depends on the murine double minute 2 protein (MDM2). Degradation and ubiquitination of p53 is dependent on MDM2, and a ternary complex between these two proteins and CBP/p300 regulates the turnover of p53 in cycling cells [67]. The CH-1 region of CBP and p300 was recently shown to display polyubiquitin ligase activity towards p53, and could therefore play a very direct role in controlling p53 levels [68]. In a third chromatin-unrelated role, CBP and p300 can acetylate two proteins involved in regulating nuclear import, the importin-α1 isoform Rch1 and importin-α7, and could therefore play a role in this process as well [69].

3. CBP, p300 and human disease

The importance of CBP and p300 is underscored by the fact that genetic alterations in their genes and functional inactivation of the proteins are strongly linked to human disease [70–73]. De novo chromosomal translocations, microdeletions and point mutations in one copy of the CBP gene result in a congenital developmental disorder named RTS, which is characterised by retarded growth and mental function, broad thumbs, broad big toes and typical facial abnormalities [74]. Furthermore, RTS patients have an increased tumour risk [75]. Haploinsufficiency of CBP is the likely cause of RTS in humans, since no clear phenotypic differences were observed between patients in which microdeletions or truncating mutations were found ([76] and references therein). In mice, heterozygous deletion or truncation of CBP also leads to an RTS-like phenotype [77–79]. We recently reported two RTS-associated mutations, one of which alters a conserved PHD finger amino acid (E1278K), while the other deletes exon 22, which encodes the central region of the PHD finger [76]. The PHD finger mutants, as well as the RTS-associated R1379P mutant described by Murata et al., all lack HAT activity [76,80]. These findings demonstrate the importance of the HAT function of CBP function in vivo and indicate that attenuating CBP HAT activity causes RTS. Interestingly, an intact bromodomain, which sometimes works in collaboration with the HAT domain [49,59,81], could also be essential, based on a recently published bromodomain mutation in an RTS patient (Y1175C [82]). At present no genetic aberrations involving p300 have been described in RTS or other human congenital disorders.

Recurrent heterozygous chromosomal translocations involving CBP (chromosome 8p11) or p300 (chromosome 22q13) are found in patients suffering from acute myeloid leukaemia (AML) (reviewed in [53]). In these balanced translocations the 5′ end of the MLL, the MOZ or the MORF gene is juxtaposed to 3′ sequences of the CBP or p300 gene, and vice-versa. While it is unknown whether the translocations observed in RTS patients result in novel fusion messages [83], virtually all translocations in AML patients are predicted to result in two reciprocal in-frame chimaeric proteins (e.g. MLL–CBP and CBP–MLL). The fusion proteins with regions of CBP or p300 at the C-terminus (MLL–CBP, MLL–p300, MOZ–CBP, MOZ–p300, MORF–CBP) appear to play the critical role in leukaemogenesis, since mRNAs encoding the reciprocal proteins (e.g. CBP–MLL) could not be detected in all patients [84,85]. Interestingly, the MOZ protein and its paralogue MORF harbour histone acetyltransferase activity themselves [86,87], while the MLL protein is a histone

methyltransferase [88,89]. In the leukaemic fusions the N-terminus of MOZ or MORF, which includes the PHD fingers and the HAT domain, is fused to CBP or p300. The region of CBP and p300 in these fusions consists of almost the full-length protein, including an intact HAT domain. Given the functional domains involved it seems likely that the fusion proteins give rise to altered histone acetylation patterns caused by mistargeting, misregulation or loss-of-function of the individual partner proteins. In agreement with this, the HAT domain of CBP was shown to be required for the MOZ–CBP mediated block of differentiation of a myeloid cell line [90]. In the MLL fusions the methyltransferase domain of MLL is lost, which might suggest that in this case a reduction in histone methyltransfersase activity is involved. Although such loss-of-function perhaps contributes to the development of leukaemia, MLL clearly requires the bromodomain and HAT domain of CBP for full in vitro transformation and induction of the leukaemic phenotype in vivo [91]. Taken together, these data favour a gain-of-function model, in which the fusion protein displays specific oncogenic activity. This is in clear contrast to the current CBP haploinsufficiency model in Rubinstein–Taybi syndrome.

Heterozygous genetic alterations in the p300 gene have been detected in primary solid tumours and tumour cell lines, mainly of epithelial origin [92–96]. Most of these sporadic mutations truncate the p300 protein, but two missense mutations have also been described in the HAT domain of p300, a glutamic acid-to-tyrosine change at position 1399 (D1399Y) in a primary colon tumour [92] and a S1650Y mutation in a pancreatic cancer cell line [93]. These mutants have been shown [97] or are predicted to lack HAT activity, and the homozygous deletion of the bromodomain (exons 15–18) in the SiHa cervical cell line is predicted to affect the ability of p300 to interact with acetylated lysine residues [98]. The functional consequences of some of the other tumour-associated mutations are unclear, since they are not located within defined functional domains. Whether these specific mutations affect the stability of the protein or alter functions of p300 that are not directly linked to its role in transcription regulation (see above) remains to be established. In the majority of cases the second allele was inactivated through deletion (loss of heterozygosity), silencing (hemizygosity) or a different mutation (compound heterozygosity). These findings qualify p300 as a classical tumour suppressor gene, according to Knudson's two-hit model [99], with a low mutation rate (e.g. 2/115 in primary tumours and 6/107 in cell lines [96]). It is currently less clear whether CBP should also be classified as a tumour suppressor gene. The predisposition to cancer in RTS patients and the fact that CBP and p300 are both targets of transforming DNA viruses (adenovirus, SV40, human papillomavirus; reviewed in [100]) suggest that CBP might also function as a tumour suppressor. However, no truncating mutations were detected in 116 primary tumours [96]. In a panel of 63 tumour cell lines 2 heterozygous mutations were found, 1 of which results in loss of HAT activity since it deletes the central 22 residues of the PHD finger (exon 22 [96]), similar to the one we found in an RTS patient [76]. The other allele was intact and functional in both cases, which argues against CBP being a classical tumour suppressor. If CBP plays a role in cancer, it could be through a dominant negative mechanism or haploinsufficiency of the gene product. The current evidence that p300 and CBP play different roles in tumourigenesis is strengthened by the observation that CBP was unable to rescue the growth of p300-deficient carcinoma cells [101].

Functional inactivation of CBP and p300 on the protein level is the second mechanism through which these acetyltransferases are (at least partly) inactivated in human disease. Some progressive neurodegenerative diseases, such as Huntington disease (HD), Kennedy disease (spinal and bulbar muscular atrophy; SBMA), dentatorubral-pallidoluysian atrophy (DRPLA) and 6 spinocerebellar ataxias (SCAs) are caused by polyglutamine-repeat expansions [102]. The mutant proteins bearing such an expanded polyglutamine tract, including the Htt protein in HD, the androgen receptor in SBMA, atrophin-1 in DRPLA and ataxin-3 in SCA3 have a tendency to form insoluble aggregates, but can also co-aggregate with polyglutamine tracts in other, normal proteins. One of the normal proteins that are sequestered in this way is the human CBP protein, which harbours a tract of 18 glutamine residues (amino acids 2199–2216) in its Q-rich C-terminus. CBP has been shown to co-localise in polyQ aggregates of expanded forms of Htt, the androgen receptor, atrophin-1 and ataxin-3, both in cell culture models and in human tissue from patients suffering from the respective diseases [103–106]. Inactivation of CBP indeed seems to be an early and causative step in polyQ toxicity, since ectopic overexpression of CBP reduces polyQ-mediated death of cultured cells [104,107]. Furthermore, the finding that progression of the neurodegenerative phenotype in Drosophila polyQ disease models is also inhibited by deacetylase inhibitors would argue that the CBP HAT function is critical for the prevention of some neurodegenerative diseases [107,108]. The p300 protein, which lacks a tract of glutamines, did not co-localise with polyQ containing aggregates in an HD model or in post-mortem brain of an HD patient [103]. The mutant Htt protein was however shown to repress the HAT activity of both CBP and p300, indicating that polyQ proteins might interfere with CBP and p300 function at more than one level [108].

An alternative mechanism of functional inactivation of the CBP and p300 proteins has recently been observed during apoptosis of neurons, a process that is observed in Alzheimer's disease (AD). In this model CBP was shown to be cleaved by caspase-6 during neurodegeneration, resulting in reduced histone acetylation levels [109]. Surprisingly, an increase in the cellular CBP levels has been associated with early-onset AD. Marambaud et al. showed

that presenilin1-mediated cleavage of N-cadherin resulted in a peptide N-Cad/CTF2, which binds CBP in the cytoplasm and promotes its proteosomal degradation. This reduction in the amount of CBP results in inhibition of CREB-mediated transcription [110]. Importantly, presenilin-1 mutations that are associated with familial AD inhibit this process, indicating that besides loss-of-function, gain-of-function of CBP may also play a role in neurodegeneration.

In summary, findings on CBP and p300 in human diseases indicate that the dosage of these proteins is essential in the regulation of normal differentiation, growth control and homeostasis in humans. Mutations in the HAT domain, as observed in RTS (CBP) and epithelial tumours (p300 and CBP), as well as the functional inactivation of the HAT function in neurodegenerative diseases argue that the ability to acetylate histones or other proteins is often essential (see Fig. 2). An intact CBP HAT domain is also essential for the induction of the leukaemic phenotype by MLL–CBP and MOZ–CBP, suggesting that mistargeting of acetyltransferase activity can trigger leukaemogenesis. Furthermore, CBP and p300 appear to be not completely redundant in some cases, since a full dosage of CBP is required to prevent RTS and neurodegenerative diseases while p300 is more important in the prevention of epithelial tumours.

4. Regulation of CBP and p300 acetyltransferase activity

The importance of the acetyltransferase function of CBP and p300 in fundamental biological processes indicates that this enzymatic activity is likely to be subject to regulation. The HAT activity of CBP and p300 is upregulated through phosphorylation by p42/p44 MAP kinase [29], cdk2 [28] or protein kinase A (PKA [111]). Conversely, protein kinase Cδ-mediated phosphorylation of a conserved serine residue at position 89 (S89) reduces the acetyltransferase activity of CBP [112]. It should be noted that S89 is the only phosphorylation site that has been confirmed in vivo, so the biological relevance of in vitro phosphorylation by p42/p44 MAP kinase, PKA and cdk2 remains to be established. Interactions with other proteins can also affect the HAT activity of CBP and p300, either in a positive or negative manner. For example, interactions with the transcription factors CAAT/enhancer-binding protein C/EBPα, the nuclear factor-erythroid derived 2 NF-E2 and the hepatocyte nuclear factor HNF-1α upregulate the HAT activity [113,114], while binding of the transcription factor PU.1 is inhibitory [115]. An intriguing question that remains to be answered is how different proteins (e.g. PU.1 and HNF-1α) that interact with the same region of CBP and p300 (CH3 region), can affect the acetyltransferase activity in opposite manners.

5. Functional similarities and differences

The high degree of homology between CBP and p300 suggests that these proteins could, at least in part, be functionally redundant. While CBP was originally isolated as a coactivator of the transcription factor CREB [116], and p300 was cloned as a protein interacting with the transforming adenoviral E1A protein [117], both proteins were subsequently shown be interchangeable for these functions [118,119]. The realization that CBP and p300 function as coactivators not only for CREB, but also for AP-1 [120] and nuclear hormone receptors [121,122] initiated a large number of studies showing that CBP and/or p300 are essential coactivators for at least 40 different transcription factors (reviewed in [27,100]). In many of these studies CBP and p300 were transiently overexpressed in cells and the two proteins were found to be interchangeable. In addition, studies with the small molecule inhibitor LysCoA have shown a block in myocyte differentiation [123] and

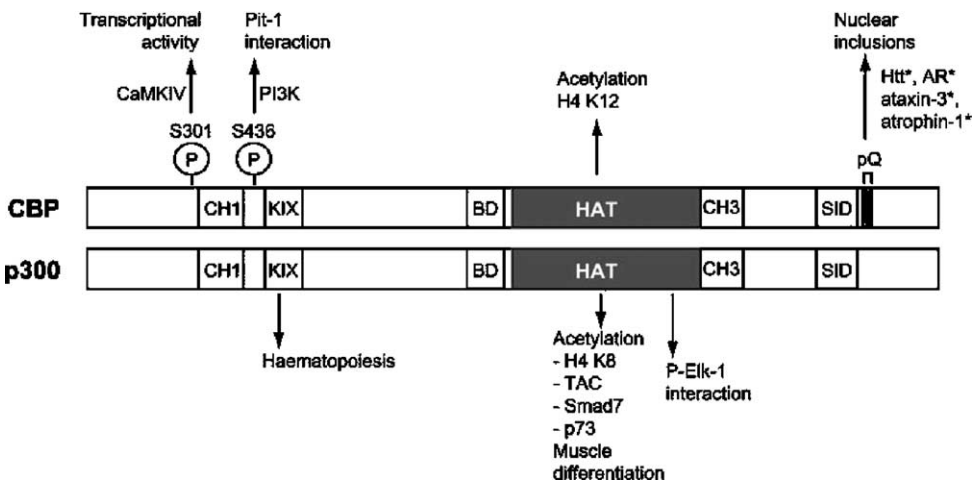

Fig. 3. Functional differences between CBP and p300. Schematic representation of the CBP and p300 proteins with functional differences indicated. See text for details.

growth inhibition and senescence in melanocytes [124], but do not distinguish between CBP and p300 since this compound inhibits the acetyltransferase activity of both [125].

However, several cell-based studies on CBP and p300 indicate that besides their functional overlap, they also harbour unique functions (Fig. 3). Using hammerhead ribozymes to specifically lower the expression of either p300 or CBP, Kawasaki et al. showed that, whereas both proteins were necessary for apoptosis and G1 arrest of F9 embryocarcinoma cells, differentiation and induction of the cell cycle inhibitor $p21^{Cip1}$ critically depended on p300, while induction of $p27^{Kip1}$ required CBP [126]. Using the same method, p300, but not CBP, was found to be essential for the cellular response to DNA damage induced by ionising radiation in MCF7 cells [127,128], and CBP and p300 were shown to be unable to mutually complement each other in the differentiation of 3T3-L1 preadipocytes into mature adipocytes [129].

In vivo studies have also indicated that CBP and p300 have shared as well as unique properties. Homozygous CBP or p300 knock-out mice die before birth ($\leq$E11.5) and both display an open neural tube defect [79,130]. A fraction of the $p300^{+/-}$ mice also die during development, while the phenotype of the double heterozygous $p300^{+/-}$;$CBP^{+/-}$ mice is invariably embryonic lethal. These findings indicate that the combined dosage of CBP and p300 is critical for embryonic development and show that CBP and p300 share some common functions that are essential for normal development. However, the phenotypes of the mice also suggested that CBP and p300 have unique functions. $p300^{-/-}$ embryo's display defective development of the heart [130], while this was not observed in $CBP^{-/-}$ embryo's [77]. Conversely, $CBP^{+/-}$ mice, but not their p300 counterparts, exhibited growth retardation and craniofacial abnormalities [77,79], reminiscent of RTS in humans (see above) and an increased incidence of haematological malignancies [79]. Interestingly, these haematological tumours displayed loss of the other CBP allele, and therefore classify CBP as a haematological tumour suppressor gene in mice, while its role in human malignancies is less clear (see above).

Because analysis of the homozygous knock-out mice is hampered by the early embryonic lethality, chimaeric mice were generated by injecting $CBP^{-/-}$ or $p300^{-/-}$ ES cells into wild type blast cysts [131]. In these chimeric animals, CBP and p300 were both found to be essential for haematopoiesis, but CBP, and not p300, is crucial for self-renewal of haematopoietic stem cells (HSC), while p300, but not CBP, is essential for HSC differentiation. Furthermore, like the $CBP^{+/-}$ mice, chimeric $CBP^{-/-}$ and $p300^{-/-}$ mice developed haematological tumours (mostly histiocytic sarcomas), indicating that both CBP and p300 are required to suppress haematological malignancies.

The studies mentioned above convincingly showed that several biological processes require either CBP or p300, but the molecular mechanisms behind these functional differences remain to be determined. Given the in vivo importance of the acetyltransferase function, it seemed likely that this domain was involved in at least some cases. The acetyltransferase function of CBP and p300 is indeed required for normal development in mice, as heterozygous inactivation of only this function causes embryonic or neonatal lethality [132,133]. Interestingly, the acetyltransferase mutation in p300 affected heart, lung and small intestine formation much more severely than the corresponding CBP mutation [132,133]. In addition, the terminal differentiation of skeletal muscle cells not only requires p300, but specifically its HAT/FAT function in vivo [133]. Given the ubiquitous expression of CBP and p300 during mouse development [19], these findings suggest that CBP and p300 may modify distinct substrates. CBP was recently shown to have a preference for acetylating K12 on histone H4, while p300 preferentially acetylates K8 on histone H4 in vivo [134]. Differential acetylation of non-histone substrates could also be important. One example of a non-histone substrate acetylated by p300, but not CBP, is the TAC complex. The TAC complex is a TBP-sans-TAFS complex consisting of TBP, the unprocessed TFIIA$\alpha\beta$ and TFIIAγ. It is found in undifferentiated cells (e.g. P19 embryocarcinoma cells), but not in differentiated cell lines such as COS-7 [135]. TAC is an acetylation substrate of p300, but not CBP, since overexpression of p300 results in the formation of TAC in COS-7 cells, and this requires the p300 HAT function and an intact bromodomain [81]. A second p300-specific acetylation substrate is Smad7, an inhibitory protein in TGF-β signalling [136]. This protein is protected from proteasome-mediated degradation by acetylation. Finally, the transcription factor p73 is acetylated specifically by p300 upon doxorubicin-induced DNA damage, resulting in specific activation of apoptotic target genes [137]. Structural differences in the enzymatic domains of the two acetyltransferases, as revealed by an extensive mutagenesis study [44], are a possible determinant of substrate specificity. Alternatively, differential in vivo interactions between acetyltransferases and their substrates might also explain the functional differences. Kasper et al. generated mice that harbour homozygous mutations in the KIX domain of either CBP or p300, designed to disrupt, for example, the interactions with the transcription factors c-Myb and CREB [138]. While $p300^{KIX/KIX}$ mice displayed multilineage defects in haematopoiesis, mice homozygous for identical mutations in CBP were essentially normal. Furthermore, the synergistic genetic interaction between c-Myb mutations and $p300^{KIX/KIX}$ suggests that the interaction between c-Myb and p300, but not CBP, is important for haematopoiesis. c-Myb has been shown to be an acetylation substrate [139,140], and it seems possible that these modifications are lost upon disruption of the substrate–enzyme interaction. How substrate specificity is achieved in vivo is currently unclear, since CBP and p300 are both able to acetylate c-Myb in vitro [140].

An indirect way to differentially regulate the HAT domains of CBP and p300 is through protein–protein interactions. For example, the hypophosphorylated form of the transcription factor Elk-1 associates with the N-terminus of p300, but not CBP. Elk-1 phosphorylation induces a novel interaction between Elk-1 and the HAT domain region of p300 (amino acid 1514–1922), resulting in increased p300 HAT activity [141]. Furthermore, two CBP-specific protein–protein interactions are due to phosphorylation of serine 436 (S436) and S301, residues that are not conserved in p300. Phosphorylation of S436 in CBP by PI-3-kinase results in increased association with the transcription factor Pit-1 [142]. Whether this also results in an increase in acetylation of Pit-1, which was shown to be an in vitro substrate [143], is currently unknown. NMDA stimulated phosphorylation of S301 in CBP by Ca^{2+}/calmodulin kinase IV (CaMKIV) results in an increase of transcriptional activity, but in this case not HAT activity [144]. Taken together, these findings demonstrate that post-translational modifications that are specific for either CBP or p300 present a potentially important mechanism for differential protein–protein interactions and subsequent regulation of the enzymatic function of these proteins.

6. Concluding remarks

The transcriptional coactivators CBP and p300 have been implicated in a plethora of transcriptional events, often based on overexpression of these proteins. However, inactivation of their genes in humans (RTS), mice or tissue culture cells indicate that their mode of action is far more specific than suggested by these overexpression studies. Furthermore, these studies also show that these proteins have common as well as unique functions, with the HAT/FAT function being critical in many cases. Interestingly, the importance of the HAT function of CBP and p300 in the control of development and cell growth is not restricted to vertebrates. In *C. elegans*, which has only one CBP/p300 homologue, inactivation of the CBP gene or inactivation of only its HAT function give rise to the same developmental defects [145,146]. In the fruitfly, which also has only one CBP/p300 homologue, wild type CBP was able to restore activation of the *wingless* gene and global acetylation of K8 on histone H4 in a CBP null fly, but HAT mutants failed to do this [147]. To determine the relative importance of the acetyltransferase functions of CBP and p300 in mammalian systems, several experimental approaches can be taken. First, in vivo studies aimed at the inactivation of the HAT domain of CBP and p300 [132,133], or, for example, the bromodomain or CH3 region, which operate in close conjunction with the HAT domain, or aimed at tissue-specific depletion, will be invaluable. Secondly, specific down-regulation of CBP or p300 by ribozymes [126] or siRNA techniques [148], followed by rescue experiments with wild type or mutated forms, will help to better define their roles in cell-based studies. Finally, the development of specific small molecules that inhibit the HAT activity of either CBP or p300, based on recently discovered compounds [125,149], would provide us with important experimental tools. Future studies employing these experimental approaches will allow us to identify those target genes that critically depend on (a full dosage of) either CBP or p300 acetyltransferase activity. Given the wide range of human diseases in which the acetyltransferase function of CBP and/or p300 have been implicated, understanding the mechanisms that regulate this enzymatic activity in vivo could help to develop novel approaches for therapeutic strategies.

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References

[1] Kingston RE, Narlikar GJ. ATP-dependent remodeling and acetylation as regulators of chromatin fluidity. Genes Dev 1999;13:2339–52.
[2] Cheung WL, Briggs SD, Allis CD. Acetylation and chromosomal functions. Curr Opin Cell Biol 2000;12:326–33.
[3] Kuo MH, Allis CD. Roles of histone acetyltransferases and deacetylases in gene regulation. Bioessays 1998;20:615–26.
[4] Kouzarides T. Histone methylation in transcriptional control. Curr Opin Genet Dev 2002;12:198–209.
[5] Cheung P, Allis CD, Sassone-Corsi P. Signaling to chromatin through histone modifications. Cell 2000;103:263–71.
[6] Shiio Y, Eisenman RN. Histone sumoylation is associated with transcriptional repression. Proc Natl Acad Sci USA 2003;100:13225–30.
[7] Jason LJ, Moore SC, Lewis JD, Lindsey G, Ausio J. Histone ubiquitination: a tagging tail unfolds? Bioessays 2002;24:166–74.
[8] Winston F, Allis CD. The bromodomain: a chromatin-targeting module? Nat Struct Biol 1999;6:601–4.
[9] Turner BM. Histone acetylation and an epigenetic code. Bioessays 2000;22:836–45.
[10] Strahl BD, Allis CD. The language of covalent histone modifications. Nature 2000;403:41–5.
[11] Agalioti T, Lomvardas S, Parekh B, Yie J, Maniatis T, Thanos D. Ordered recruitment of chromatin modifying and general transcription factors to the IFN-beta promoter. Cell 2000;103:667–78.
[12] Cosma MP, Tanaka T, Nasmyth K. Ordered recruitment of transcription and chromatin remodeling factors to a cell cycle- and developmentally regulated promoter. Cell 1999;97:299–311.
[13] Martens JH, Verlaan M, Kalkhoven E, Zantema A. Cascade of distinct histone modifications during collagenase gene activation. Mol Cell Biol 2003;23:1808–16.
[14] Shang Y, Hu X, DiRenzo J, Lazar MA, Brown M. Cofactor dynamics and sufficiency in estrogen receptor-regulated transcription. Cell 2000;103:843–52.

[15] Soutoglou E, Talianidis I. Coordination of PIC assembly and chromatin remodeling during differentiation-induced gene activation. Science 2002;295:1901–4.
[16] Arany Z, Sellers WR, Livingston DM, Eckner R. E1A-associated p300 and CREB-associated CBP belong to a conserved family of coactivators. Cell 1994;77:799–800.
[17] Yuan LW, Giordano A. Acetyltransferase machinery conserved in p300/CBP-family proteins. Oncogene 2002;21:2253–60.
[18] Bordoli L, Netsch M, Luthi U, Lutz W, Eckner R. Plant orthologs of p300/CBP: conservation of a core domain in metazoan p300/CBP acetyltransferase-related proteins. Nucl Acids Res 2001;29:589–97.
[19] Partanen A, Motoyama J, Hui CC. Developmentally regulated expression of the transcriptional cofactors/histone acetyltransferases CBP and p300 during mouse embryogenesis. Int J Dev Biol 1999;43:487–94.
[20] Yuan W, Condorelli G, Caruso M, Felsani A, Giordano A. Human p300 protein is a coactivator for the transcription factor MyoD. J Biol Chem 1996;271:9009–13.
[21] Kwok RP, Lundblad JR, Chrivia JC, Richards JP, Bachinger HP, Brennan RG, et al. Nuclear protein CBP is a coactivator for the transcription factor CREB. Nature 1994;370:223–6.
[22] Neish AS, Anderson SF, Schlegel BP, Wei W, Parvin JD. Factors associated with the mammalian RNA polymerase II holoenzyme. Nucl Acids Res 1998;26:847–53.
[23] Nakajima T, Uchida C, Anderson SF, Lee CG, Hurwitz J, Parvin JD, et al. RNA helicase A mediates association of CBP with RNA polymerase II. Cell 1997;90:1107–12.
[24] Nakajima T, Uchida C, Anderson SF, Parvin JD, Montminy M. Analysis of a cAMP-responsive activator reveals a two-component mechanism for transcriptional induction via signal-dependent factors. Genes Dev 1997;11:738–47.
[25] Cho H, Orphanides G, Sun X, Yang XJ, Ogryzko V, Lees E, et al. A human RNA polymerase II complex containing factors that modify chromatin structure. Mol Cell Biol 1998;18:5355–63.
[26] Chan HM, La Thangue NB. p300/CBP proteins: HATs for transcriptional bridges and scaffolds. J Cell Sci 2001;114:2363–73.
[27] Vo N, Goodman RH. CREB-binding protein and p300 in transcriptional regulation. J Biol Chem 2001;276:13505–8.
[28] Ait-Si-Ali S, Ramirez S, Barre FX, Dkhissi F, Magnaghi-Jaulin L, Girault JA, et al. Histone acetyltransferase activity of CBP is controlled by cycle-dependent kinases and oncoprotein E1A. Nature 1998;396:184–6.
[29] Ait-Si-Ali S, Carlisi D, Ramirez S, Upegui-Gonzalez LC, Duquet A, Robin P, et al. Phosphorylation by p44 MAP Kinase/ERK1 stimulates CBP histone acetyl transferase activity in vitro. Biochem Biophys Res Commun 1999;262:157–62.
[30] Janknecht R, Nordheim A. MAP kinase-dependent transcriptional coactivation by Elk-1 and its cofactor CBP. Biochem Biophys Res Commun 1996;228:831–7.
[31] Girdwood D, Bumpass D, Vaughan OA, Thain A, Anderson LA, Snowden AW, et al. P300 transcriptional repression is mediated by SUMO modification. Mol Cell 2003;11:1043–54.
[32] Xu W, Chen H, Du K, Asahara H, Tini M, Emerson BM, et al. A transcriptional switch mediated by cofactor methylation. Science 2001;294:2507–11.
[33] Chevillard-Briet M, Trouche D, Vandel L. Control of CBP co-activating activity by arginine methylation. EMBO J 2002;21:5457–66.
[34] Ogryzko VV, Schiltz RL, Russanova V, Howard BH, Nakatani Y. The transcriptional coactivators p300 and CBP are histone acetyltransferases. Cell 1996;87:953–9.
[35] Bannister AJ, Kouzarides T. The CBP co-activator is a histone acetyltransferase. Nature 1996;384:641–3.
[36] Kundu TK, Palhan VB, Wang Z, An W, Cole PA, Roeder RG. Activator-dependent transcription from chromatin in vitro involving targeted histone acetylation by p300. Mol Cell 2000;6:551–61.
[37] Martinez-Balbas MA, Bannister AJ, Martin K, Haus-Seuffert P, Meisterernst M, Kouzarides T. The acetyltransferase activity of CBP stimulates transcription. EMBO J 1998;17:2886–93.
[38] Neuwald AF, Landsman D. GCN5-related histone N-acetyltransferases belong to a diverse superfamily that includes the yeast SPT10 protein. Trends Biochem Sci 1997;22:154–5.
[39] Yan Y, Barlev NA, Haley RH, Berger SL, Marmorstein R. Crystal structure of yeast esa1 suggests a unified mechanism for catalysis and substrate binding by histone acetyltransferases. Mol Cell 2000;6:1195–205.
[40] Marmorstein R, Roth SY. Histone acetyltransferases: function, structure, and catalysis. Curr Opin Genet Dev 2001;11:155–61.
[41] Aasland R, Gibson TJ, Stewart AF. The PHD finger: implications for chromatin-mediated transcriptional regulation. Trends Biochem Sci 1995;20:56–9.
[42] Saha V, Chaplin T, Gregorini A, Ayton P, Young BD. The leukemia-associated-protein (LAP) domain, a cysteine-rich motif, is present in a wide range of proteins, including MLL, AF10, and MLLT6 proteins. Proc Natl Acad Sci USA 1995;92:9737–41.
[43] Koken MH, Saib A, de The H. A C4HC3 zinc finger motif. CR Acad Sci III 1995;318:733–9.
[44] Bordoli L, Husser S, Luthi U, Netsch M, Osmani H, Eckner R. Functional analysis of the p300 acetyltransferase domain: the PHD finger of p300 but not of CBP is dispensable for enzymatic activity. Nucl Acids Res 2001;29:4462–71.
[45] Kalkhoven E, Teunissen H, Houweling A, Verrijzer CP, Zantema A. The PHD type zinc finger is an integral part of the CBP acetyltransferase domain. Mol Cell Biol 2002;22:1961–70.
[46] Jeanmougin F, Wurtz JM, Le Douarin B, Chambon P, Losson R. The bromodomain revisited. Trends Biochem Sci 1997;22:151–3.
[47] Dhalluin C, Carlson JE, Zeng L, He C, Aggarwal AK, Zhou MM. Structure and ligand of a histone acetyltransferase bromodomain. Nature 1999;399:491–6.
[48] Jacobson RH, Ladurner AG, King DS, Tjian R. Structure and function of a human TAFII250 double bromodomain module. Science 2000;288:1422–5.
[49] Manning ET, Ikehara T, Ito T, Kadonaga JT, Kraus WL. p300 forms a stable, template-committed complex with chromatin: role for the bromodomain. Mol Cell Biol 2001;21:3876–87.
[50] Ragvin A, Valvatne H, Erdal S, Arskog V, Tufteland KR, Breen K, et al. Nucleosome binding by the bromodomain and PHD finger of the transcriptional cofactor p300. J Mol Biol 2004;337:773–88.
[51] Schiltz RL, Mizzen CA, Vassilev A, Cook RG, Allis CD, Nakatani Y. Overlapping but distinct patterns of histone acetylation by the human coactivators p300 and PCAF within nucleosomal substrates. J Biol Chem 1999;274:1189–92.
[52] Sterner DE, Berger SL. Acetylation of histones and transcription-related factors. Microbiol Mol Biol Rev 2000;64:435–59.
[53] Yang XJ. The diverse superfamily of lysine acetyltransferases and their roles in leukemia and other diseases. Nucl Acids Res 2004;32:959–76.
[54] Chen H, Lin RJ, Xie W, Wilpitz D, Evans RM. Regulation of hormone-induced histone hyperacetylation and gene activation via acetylation of an acetylase. Cell 1999;98:675–86.
[55] Munshi N, Merika M, Yie J, Senger K, Chen G, Thanos D. Acetylation of HMG I(Y) by CBP turns off IFN beta expression by disrupting the enhanceosome. Mol Cell 1998;2:457–67.
[56] Soutoglou E, Katrakili N, Talianidis I. Acetylation regulates transcription factor activity at multiple levels. Mol Cell 2000;5:745–51.
[57] Martinez-Balbas MA, Bauer UM, Nielsen SJ, Brehm A, Kouzarides T. Regulation of E2F1 activity by acetylation. EMBO J 2000;19:662–71.
[58] Korzus E, Torchia J, Rose DW, Xu L, Kurokawa R, McInerney EM, et al. Transcription factor-specific requirements for coactivators and their acetyltransferase functions. Science 1998;279:703–7.

[59] Kraus WL, Manning ET, Kadonaga JT. Biochemical analysis of distinct activation functions in p300 that enhance transcription initiation with chromatin templates. Mol Cell Biol 1999;19: 8123–35.
[60] Kurokawa R, Kalafus D, Ogliastro MH, Kioussi C, Xu L, Torchia J, et al. Differential use of CREB binding protein–coactivator complexes. Science 1998;279:700–3.
[61] Hasan S, Hassa PO, Imhof R, Hottiger MO. Transcription coactivator p300 binds PCNA and may have a role in DNA repair synthesis. Nature 2001;410:387–91.
[62] Hasan S, Stucki M, Hassa PO, Imhof R, Gehrig P, Hunziker P, et al. Regulation of human flap endonuclease-1 activity by acetylation through the transcriptional coactivator p300. Mol Cell 2001;7:1221–31.
[63] Hasan S, El Andaloussi N, Hardeland U, Hassa PO, Burki C, Imhof R, et al. Acetylation regulates the DNA end-trimming activity of DNA polymerase beta. Mol Cell 2002;10:1213–22.
[64] Tini M, Benecke A, Um SJ, Torchia J, Evans RM, Chambon P. Association of CBP/p300 acetylase and thymine DNA glycosylase links DNA repair and transcription. Mol Cell 2002;9:265–77.
[65] Perkins ND, Felzien LK, Betts JC, Leung K, Beach DH, Nabel GJ. Regulation of NF-kappaB by cyclin-dependent kinases associated with the p300 coactivator. Science 1997;275:523–7.
[66] Ait-Si-Ali S, Polesskaya A, Filleur S, Ferreira R, Duquet A, Robin P, et al. CBP/p300 histone acetyl-transferase activity is important for the G1/S transition. Oncogene 2000;19:2430–7.
[67] Grossman SR, Perez M, Kung AL, Joseph M, Mansur C, Xiao ZX, et al. Livingston DM, p300/MDM2 complexes participate in MDM2-mediated p53 degradation. Mol Cell 1998;2:405–15.
[68] Grossman SR, Deato ME, Brignone C, Chan HM, Kung AL, Tagami H, et al. Polyubiquitination of p53 by a ubiquitin ligase activity of p300. Science 2003;300:342–4.
[69] Bannister AJ, Miska EA, Gorlich D, Kouzarides T. Acetylation of importin-alpha nuclear import factors by CBP/p300. Curr Biol 2000S;10:467–70.
[70] Klochendler-Yeivin A, Yaniv M. Chromatin modifiers and tumor suppression. Biochim Biophys Acta 2001;1551:M1–M10.
[71] Timmermann S, Lehrmann H, Polesskaya A, Harel-Bellan A. Histone acetylation and disease. Cell Mol Life Sci 2001;58:728–36.
[72] Cairns BR. Emerging roles for chromatin remodeling in cancer biology. Trends Cell Biol 2001;11:S15–21.
[73] Giles RH, Peters DJ, Breuning MH. Conjunction dysfunction: CBP/p300 in human disease. Trends Genet 1998;14:178–83.
[74] Rubinstein JH, Taybi H. Broad thumbs and toes and facial abnormalities. Am J Dis Child 1963;105:588–608.
[75] Miller RW, Rubinstein JH. Tumors in Rubinstein–Taybi syndrome. Am J Med Genet 1995;56:112–5.
[76] Kalkhoven E, Roelfsema JH, Teunissen H, den Boer A, Ariyurek Y, Zantema A, et al. Loss of CBP acetyltransferase activity by PHD finger mutations in Rubinstein–Taybi syndrome. Hum Mol Genet 2003;12:441–50.
[77] Tanaka Y, Naruse I, Maekawa T, Masuya H, Shiroishi T, Ishii S. Abnormal skeletal patterning in embryos lacking a single Cbp allele: a partial similarity with Rubinstein–Taybi syndrome. Proc Natl Acad Sci USA 1997;94:10215–20.
[78] Oike Y, Hata A, Mamiya T, Kaname T, Noda Y, Suzuki M, et al. Truncated CBP protein leads to classical Rubinstein–Taybi syndrome phenotypes in mice: implications for a dominant-negative mechanism. Hum Mol Genet 1999;8:387–96.
[79] Kung AL, Rebel VI, Bronson RT, Ch'ng LE, Sieff CA, Livingston DM, et al. Gene dose-dependent control of hematopoiesis and hematologic tumor suppression by CBP. Genes Dev 2000;14:272–7.
[80] Murata T, Kurokawa R, Krones A, Tatsumi K, Ishii M, Taki T, et al. Defect of histone acetyltransferase activity of the nuclear transcriptional coactivator CBP in Rubinstein–Taybi syndrome. Hum Mol Genet 2001;10:1071–6.
[81] Mitsiou DJ, Stunnenberg HG. p300 is involved in formation of the TBP-TFIIA-containing basal transcription complex, TAC. EMBO J 2003;22:4501–11.
[82] Bartsch O, Locher K, Meinecke P, Kress W, Seemanova E, Wagner A, et al. Molecular studies in 10 cases of Rubinstein–Taybi syndrome, including a mild variant showing a missense mutation in codon 1175 of CREBBP. J Med Genet 2002;39:496–501.
[83] Petrij F, Giles RH, Dauwerse HG, Saris JJ, Hennekam RC, Masuno M, et al. Rubinstein–Taybi syndrome caused by mutations in the transcriptional co-activator CBP. Nature 1995;376:348–51.
[84] Sobulo OM, Borrow J, Tomek R, Reshmi S, Harden A, Schlegelberger B, et al. MLL is fused to CBP, a histone acetyltransferase, in therapy-related acute myeloid leukemia with a t(11;16)(q23;p13.3). Proc Natl Acad Sci USA 1997;94:8732–7.
[85] Taki T, Sako M, Tsuchida M, Hayashi Y. The t(11;16)(q23;p13) translocation in myelodysplastic syndrome fuses the MLL gene to the CBP gene. Blood 1997;89:3945–50.
[86] Champagne N, Bertos NR, Pelletier N, Wang AH, Vezmar M, Yang Y, et al. Identification of a human histone acetyltransferase related to monocytic leukemia zinc finger protein. J Biol Chem 1999;274: 28528–36.
[87] Champagne N, Pelletier N, Yang XJ. The monocytic leukemia zinc finger protein MOZ is a histone acetyltransferase. Oncogene 2001;20:404–9.
[88] Nakamura T, Mori T, Tada S, Krajewski W, Rozovskaia T, Wassell R, et al. ALL-1 is a histone methyltransferase that assembles a supercomplex of proteins involved in transcriptional regulation. Mol Cell 2002;10:1119–28.
[89] Milne TA, Briggs SD, Brock HW, Martin ME, Gibbs D, Allis CD, et al. MLL targets SET domain methyltransferase activity to Hox gene promoters. Mol Cell 2002;10:1107–17.
[90] Kitabayashi I, Aikawa Y, Nguyen LA, Yokoyama A, Ohki M. Activation of AML1-mediated transcription by MOZ and inhibition by the MOZ–CBP fusion protein. EMBO J 2001;20:7184–96.
[91] Lavau C, Du C, Thirman M, Zeleznik-Le N. Chromatin-related properties of CBP fused to MLL generate a myelodysplastic-like syndrome that evolves into myeloid leukemia. EMBO J 2000;19:4655–64.
[92] Muraoka M, Konishi M, Kikuchi-Yanoshita R, Tanaka K, Shitara N, Chong JM, et al. p300 gene alterations in colorectal and gastric carcinomas. Oncogene 1996;12:1565–9.
[93] Gayther SA, Batley SJ, Linger L, Bannister A, Thorpe K, Chin SF, et al. Mutations truncating the EP300 acetylase in human cancers. Nat Genet 2000;24:300–3.
[94] Ionov Y, Nowak N, Perucho M, Markowitz S, Cowell JK. Manipulation of nonsense mediated decay identifies gene mutations in colon cancer cells with microsatellite instability. Oncogene 2004; 23:639–45.
[95] Ionov Y, Matsui SI, Cowell JK. A role for p300/CREB binding protein genes in promoting cancer progression in colon cancer cell lines with microsatellite instability. Proc Natl Acad Sci USA 2004;101:1273–8.
[96] Ozdag H, Batley SJ, Forsti A, Iyer NG, Daigo Y, Boutell J, et al. Mutation analysis of CBP and PCAF reveals rare inactivating mutations in cancer cell lines but not in primary tumours. Brit J Cancer 2002;87:1162–5.
[97] Ito A, Lai CH, Zhao X, Saito S, Hamilton MH, Appella E, et al. p300/CBP-mediated p53 acetylation is commonly induced by p53-activating agents and inhibited by MDM2. EMBO J 2001;20:1331–40.
[98] Ohshima T, Suganuma T, Ikeda M. A novel mutation lacking the bromodomain of the transcriptional coactivator p300 in the SiHa cervical carcinoma cell line. Biochem Biophys Res Commun 2001;281:569–75.
[99] Knudson Jr AG. Mutation and cancer: statistical study of retinoblastoma. Proc Natl Acad Sci USA 1971;68:820–3.
[100] Goodman RH, Smolik S. CBP/p300 in cell growth, transformation, and development. Genes Dev 2000;14:1553–77.

[101] Suganuma T, Kawabata M, Ohshima T, Ikeda MA. Growth suppression of human carcinoma cells by reintroduction of the p300 coactivator. Proc Natl Acad Sci USA 2002;99:13073–8.
[102] Zoghbi HY, Orr HT. Glutamine repeats and neurodegeneration. Annu Rev Neurosci 2000;23:217–47.
[103] Nucifora Jr FC, Sasaki M, Peters MF, Huang H, Cooper JK, Yamada M, et al. Interference by huntingtin and atrophin-1 with cbp-mediated transcription leading to cellular toxicity. Science 2001;291:2423–38.
[104] McCampbell A, Taylor JP, Taye AA, Robitschek J, Li M, Walcott J, et al. CREB-binding protein sequestration by expanded polyglutamine. Hum Mol Genet 2000;9:2197–202.
[105] Yamada M, Wood JD, Shimohata T, Hayashi S, Tsuji S, Ross CA, et al. Widespread occurrence of intranuclear atrophin-1 accumulation in the central nervous system neurons of patients with dentatorubral-pallidoluysian atrophy. Ann Neurol 2001;49:14–23.
[106] Shimohata T, Nakajima T, Yamada M, Uchida C, Onodera O, Naruse S, et al. Expanded polyglutamine stretches interact with TAFII130, interfering with CREB-dependent transcription. Nat Genet 2000;26:29–36.
[107] Taylor JP, Taye AA, Campbell C, Kazemi-Esfarjani P, Fischbeck KH, Min KT. Aberrant histone acetylation, altered transcription, and retinal degeneration in a Drosophila model of polyglutamine disease are rescued by CREB-binding protein. Genes Dev 2003;17:1463–8.
[108] Steffan JS, Bodai L, Pallos J, Poelman M, McCampbell A, Apostol BL, et al. Histone deacetylase inhibitors arrest polyglutamine-dependent neurodegeneration in Drosophila. Nature 2001;413:739–43.
[109] Rouaux C, Jokic N, Mbebi C, Boutillier S, Loeffler JP, Boutillier AL. Critical loss of CBP/p300 histone acetylase activity by caspase-6 during neurodegeneration. EMBO J 2003;22:6537–49.
[110] Marambaud P, Wen PH, Dutt A, Shioi J, Takashima A, Siman R, et al. A CBP binding transcriptional repressor produced by the PS1/epsilon-cleavage of N-cadherin is inhibited by PS1 FAD mutations. Cell 2003;114:635–45.
[111] Brouillard F, Cremisi CE. Concomitant increase of histone acetyltransferase activity and degradation of p300 during retinoic acid-induced differentiation of F9 cells. J Biol Chem 2003;278:39509–16.
[112] Yuan LW, Soh JW, Weinstein IB. Inhibition of histone acetyltransferase function of p300 by PKCdelta. Biochim Biophys Acta 2002;1592:205–11.
[113] Chen CJ, Deng Z, Kim AY, Blobel GA, Lieberman PM. Stimulation of CREB binding protein nucleosomal histone acetyltransferase activity by a class of transcriptional activators. Mol Cell Biol 2001;21:476–87.
[114] Soutoglou E, Viollet B, Vaxillaire M, Yaniv M, Pontoglio M, Talianidis I. Transcription factor-dependent regulation of CBP and P/CAF histone acetyltransferase activity. EMBO J 2001;20:1984–92.
[115] Hong W, Kim AY, Ky S, Rakowski C, Seo SB, Chakravarti D, et al. Inhibition of CBP-mediated protein acetylation by the Ets family oncoprotein PU.1. Mol Cell Biol 2002;22:3729–43.
[116] Chrivia JC, Kwok RP, Lamb N, Hagiwara M, Montminy MR, Goodman RH. Phosphorylated CREB binds specifically to the nuclear protein CBP. Nature 1993;365:855–9.
[117] Eckner R, Ewen ME, Newsome D, Gerdes M, DeCaprio JA, Lawrence JB, et al. Molecular cloning and functional analysis of the adenovirus E1A-associated 300-kDa protein (p300) reveals a protein with properties of a transcriptional adaptor. Genes Dev 1994;8:869–84.
[118] Arany Z, Newsome D, Oldread E, Livingston DM, Eckner R. A family of transcriptional adaptor proteins targeted by the E1A oncoprotein. Nature 1995;374:81–4.
[119] Lee JS, Zhang X, Shi Y. Differential interactions of the CREB/ATF family of transcription factors with p300 and adenovirus E1A. J Biol Chem 1996;271:17666–74.
[120] Bannister AJ, Kouzarides T. CBP-induced stimulation of c-Fos activity is abrogated by E1A. EMBO J 1995;14:4758–62.
[121] Kamei Y, Xu L, Heinzel T, Torchia J, Kurokawa R, Gloss B, et al. A CBP integrator complex mediates transcriptional activation and AP-1 inhibition by nuclear receptors. Cell 1996;85:403–14.
[122] Chakravarti D, LaMorte VJ, Nelson MC, Nakajima T, Schulman IG, Juguilon H, et al. Role of CBP/P300 in nuclear receptor signalling. Nature 1996;383:99–103.
[123] Polesskaya A, Naguibneva I, Fritsch L, Duquet A, Ait-Si-Ali S, Robin P, et al. CBP/p300 and muscle differentiation: no HAT, no muscle. EMBO J 2001;20:6816–25.
[124] Bandyopadhyay D, Okan NA, Bales E, Nascimento L, Cole PA, Medrano EE. Down-regulation of p300/CBP histone acetyltransferase activates a senescence checkpoint in human melanocytes. Cancer Res 2002;62:6231–9.
[125] Lau OD, Kundu TK, Soccio RE, Ait-Si-Ali S, Khalil EM, Vassilev A, et al. HATs off: selective synthetic inhibitors of the histone acetyltransferases p300 and PCAF. Mol Cell 2000;5:589–95.
[126] Kawasaki H, Eckner R, Yao TP, Taira K, Chiu R, Livingston DM, et al. Distinct roles of the co-activators p300 and CBP in retinoic-acid-induced F9-cell differentiation. Nature 1998;393:284–9.
[127] Yuan ZM, Huang Y, Ishiko T, Nakada S, Utsugisawa T, Shioya H, et al. Function for p300 and not CBP in the apoptotic response to DNA damage. Oncogene 1999;18:5714–7.
[128] Yuan ZM, Huang Y, Ishiko T, Nakada S, Utsugisawa T, Shioya H, et al. Role for p300 in stabilization of p53 in the response to DNA damage. J Biol Chem 1999;274:1883–6.
[129] Takahashi N, Kawada T, Yamamoto T, Goto T, Taimatsu A, Aoki N, et al. Overexpression and ribozyme-mediated targeting of transcriptional coactivators CREB-binding protein and p300 revealed their indispensable roles in adipocyte differentiation through the regulation of peroxisome proliferator-activated receptor gamma. J Biol Chem 2002;277:16906–12.
[130] Yao TP, Oh SP, Fuchs M, Zhou ND, Ch'ng LE, Newsome D, et al. Gene dosage-dependent embryonic development and proliferation defects in mice lacking the transcriptional integrator p300. Cell 1998;93:361–72.
[131] Rebel VI, Kung AL, Tanner EA, Yang H, Bronson RT, Livingston DM. Distinct roles for CREB-binding protein and p300 in hematopoietic stem cell self-renewal. Proc Natl Acad Sci USA 2002;99:14789–94.
[132] Shikama N, Lutz W, Kretzschmar R, Sauter N, Roth JF, Marino S, et al. Essential function of p300 acetyltransferase activity in heart, lung and small intestine formation. EMBO J 2003;22:5175–85.
[133] Roth JF, Shikama N, Henzen C, Desbaillets I, Lutz W, Marino S, et al. Differential role of p300 and CBP acetyltransferase during myogenesis: p300 acts upstream of MyoD and Myf5. EMBO J 2003;22:5186–96.
[134] McManus KJ, Hendzel MJ. Quantitative analysis of CBP- and P300-induced histone acetylations in vivo using native chromatin. Mol Cell Biol 2003;23:7611–27.
[135] Mitsiou DJ, Stunnenberg HG. TAC, a TBP-sans-TAFs complex containing the unprocessed TFIIAalphabeta precursor and the TFIIAgamma subunit. Mol Cell 2000;6:527–37.
[136] Gronroos E, Hellman U, Heldin CH, Ericsson J. Control of Smad7 stability by competition between acetylation and ubiquitination. Mol Cell 2002;10:483–93.
[137] Costanzo A, Merlo P, Pediconi N, Fulco M, Sartorelli V, Cole PA, et al. DNA damage-dependent acetylation of p73 dictates the selective activation of apoptotic target genes. Mol Cell 2002;9:175–86.
[138] Kasper LH, Boussouar F, Ney PA, Jackson CW, Rehg J, van Deursen JM, et al. A transcription-factor-binding surface of coactivator p300 is required for haematopoiesis. Nature 2002;419:738–43.
[139] Tomita A, Towatari M, Tsuzuki S, Hayakawa F, Kosugi H, Tamai K, et al. c-Myb acetylation at the carboxyl-terminal conserved domain by transcriptional co-activator p300. Oncogene 2000;19:444–51.

[140] Sano Y, Ishii S. Increased affinity of c-Myb for CREB-binding protein (CBP) after CBP-induced acetylation. J Biol Chem 2001;276:3674–82.
[141] Li QJ, Yang SH, Maeda Y, Sladek FM, Sharrocks AD, Martins-Green M. MAP kinase phosphorylation-dependent activation of Elk-1 leads to activation of the co-activator p300. EMBO J 2003;22:281–91.
[142] Zanger K, Radovick S, Wondisford FE. CREB binding protein recruitment to the transcription complex requires growth factor-dependent phosphorylation of its GF box. Mol Cell 2001;7:551–8.
[143] Perissi V, Dasen JS, Kurokawa R, Wang Z, Korzus E, Rose DW, et al. Factor-specific modulation of CREB-binding protein acetyltransferase activity. Proc Natl Acad Sci USA 1999;96:3652–7.
[144] Impey S, Fong AL, Wang Y, Cardinaux JR, Fass DM, Obrietan K, et al. Phosphorylation of CBP mediates transcriptional activation by neural activity and CaM kinase IV. Neuron 2002;34:235–44.
[145] Shi Y, Mello C. A CBP/p300 homolog specifies multiple differentiation pathways in *Caenorhabditis elegans*. Genes Dev 1998;12:943–55.
[146] Victor M, Bei Y, Gay F, Calvo D, Mello C, Shi Y. HAT activity is essential for CBP-1-dependent transcription and differentiation in *Caenorhabditis elegans*. EMBO Rep 2002;3:50–5.
[147] Ludlam WH, Taylor MH, Tanner KG, Denu JM, Goodman RH, Smolik SM. The acetyltransferase activity of CBP is required for wingless activation and H4 acetylation in *Drosophila melanogaster*. Mol Cell Biol 2002;22:3832–41.
[148] Elbashir SM, Harborth J, Lendeckel W, Yalcin A, Weber K, Tuschl T. Duplexes of 21-nucleotide RNAs mediate RNA interference in cultured mammalian cells. Nature 2001;411:494–8.
[149] Balasubramanyam K, Swaminathan V, Ranganathan A, Kundu TK. Small molecule modulators of histone acetyltransferase p300. J Biol Chem 2003;278:19134–40.