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Review

The versatile functions of the transcriptional coactivators p300 and CBP and their roles in disease

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Summary. p300 and CBP are highly homologous coactivators which promote gene transcription by bridging between DNA-binding transcription factors and the basal transcription machinery, by providing a scaffold for integrating transcription factors, and by modifying transcription factors and chromatin through acetylation. The p300/CBP cofactors are involved in a plethora of physiological processes, and their activity is essential for embryogenesis. Chromosomal translocations affecting the *p300* and *Cbp* genes are the cause of hematological malignancies, and *Cbp* haploinsufficiency is a hallmark of the Rubinstein-Taybi syndrome. In addition, mutations in the *Cbp* or *p300* gene, accompanied by loss of the other allele, have been found in various kinds of tumors. Furthermore, inhibition of CBP and p300 function in neurodegenerative diseases caused by polyglutamine expansion may be an underlying cause for cytotoxicity. Approaches to modulate p300/CBP function may be instrumental in the development of novel therapies directed against viral infections, cancer and neurodegenerative diseases.

Key words: CBP, Coactivator, p300, Transcription regulation, Tumor suppressor

Introduction

The human CREB-binding protein (CBP) and p300 are highly homologous proteins that are well conserved amongst mammals. Homologs of p300/CBP can be found in organisms such as *Drosophila* (Akimaru et al., 1997) and *Caenorhabditis* (Shi and Mello, 1998), and even the plant *Arabidopsis thaliana* encodes for p300/CBP-like polypeptides (Bordoli et al., 2001). However, no p300/CBP homologs are present in prokaryotes or yeast.

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CBP was identified in 1993 as an interaction partner for the CREB transcription factor (Chrivia et al., 1993), and soon thereafter, *p300* cDNA was cloned encoding the 300 kDa protein known to be associated with the adenoviral protein E1A (Eckner et al., 1994). Both CBP and p300 have originally been described as transcriptional coactivators that bridge DNA-binding transcription factors to components of the basal transcriptional machinery (see Fig. 1A), including the TATA-box-binding protein (TBP) (Yuan et al., 1996), TFIIB (Kwok et al., 1994) and, via RNA helicase A, also RNA polymerase II (Nakajima et al., 1997). During the last decade, a plethora of transcription factors have been found to physically interact with p300/CBP and to be dependent on these coactivators for their function (Janknecht and Hunter, 1996a,b, 1999; Shikama et al., 1997; Giles et al., 1998; Goodman and Smolik, 2000; Chan and La Thangue, 2001; Vo and Goodman, 2001). Fig. 2 shows a non-comprehensive selection of those p300/CBP-interacting factors and their binding to specific regions in p300/CBP.

Apart from acting as bridging molecules between specific DNA-binding transcription factors and the basal transcription machinery, p300/CBP can also serve the function of a scaffold, thereby bringing together a variety of different proteins (see Fig. 1B). The huge size of p300/CBP of over 2400 amino acids allows many different interaction surfaces to form, thus enabling p300/CBP to bind to various proteins at the same time. One example of a scaffolding function has been revealed in the regulation of the *interferon-ß* gene, where p300/CBP mediate the simultaneous recruitment of several transcription factors into an enhanceosome (Kim et al., 1998; Merika et al., 1998). Another example is given by nuclear hormone receptors and the cognate nuclear hormone receptor coactivator family, which all

Abbreviations: CBP: CREB-binding protein; HAT: Histone acetyltransferase; MAPK: Mitogen-activated protein kinase; MLL: Mixed lineage leukemia; MORF: MOZ-related factor; MOZ: Monocytic leukemia zinc finger protein; PKA: Protein kinase A; PKC: Protein kinase C; pRb: Retinoblastoma tumor suppressor protein; TBP: TATA-box-binding protein; SV40: Simian Virus 40

bind to p300/CBP (Xu et al., 1999). Furthermore, p300/CBP interact with protein kinases such as the mitogen-activated protein kinases (MAPKs) (Liu et al., 1999b) and the cyclin E-Cdk2 complex (Perkins et al., 1997), which may promote the phosphorylation of p300/CBP-interacting transcription factors such as ER81 (Papoutsopoulou and Janknecht, 2000; Bosc et al., 2001) and E2F family members (Morris et al., 2000).

Finally, p300/CBP are enzymes that catalyze the transfer of acetyl residues from acetyl-coenzyme A to the ε-amino group of lysine residues (Bannister and Kouzarides, 1996; Ogryzko et al., 1996). This acetyltransferase function of p300/CBP has profound consequences for nucleosomal structure and the activity of transcription factors, and thereby affects gene activity in multiple ways (see Fig. 1C).

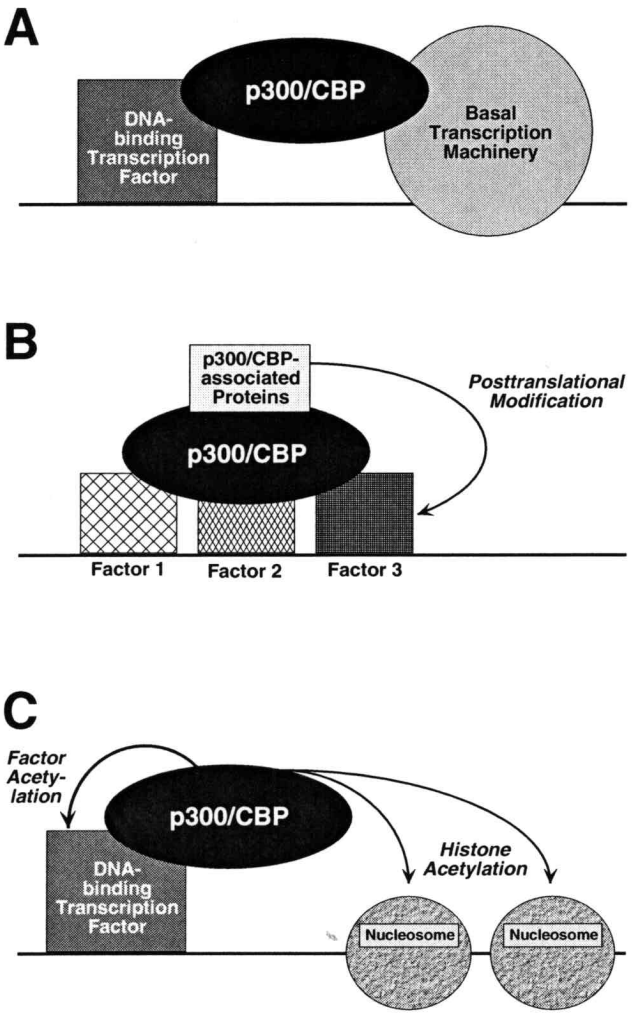

Fig. 1. Mechanisms of p300/CBP transcriptional coactivation. **A.** p300/CBP as bridges between DNA-bound transcription factors and the basal transcription machinery located at the start site of transcription. **B.** p300/CBP as scaffolds which allow the recruitment of different transcription factors to enhancer or gene promoter elements. Individually, the transcription factors may not stably bind to DNA, but tethered together by p300/CBP they do. p300/CBP-associated proteins may additionally modify transcription factors in the scaffold, e.g. by phosphorylation or acetylation. **C.** p300/CBP as acetyltransferases. Acetylation of nucleosomal proteins or DNA-binding transcription factors promotes initiation and elongation of gene transcription.

Structure of p300/CBP

The human CBP protein spans 2442 amino acids, and its paralog p300 2414. Overall, these two proteins are 61% identical and 72% similar at the amino acid level, indicating that the *Cbp* and *p300* genes have been derived from a common ancestor by gene duplication. Consistent with this high degree of sequence similarity, these two proteins are most often functionally interchangeable. Several structural and functional domains have been identified in p300/CBP. Three cysteine/histidine-rich regions (see Fig. 2, CH1 to CH3) are present in p300/CBP, and they most likely are zinc-binding modules. Indeed, the CH1 and CH3 regions contain each two zinc bundle motifs of the sequence Cys-X_4-Cys-X_8-His-X_3-Cys or Cys-X_2-Cys-X_9-His-X_3-Cys, whose folding appear to be zinc-dependent (Newton et al., 2000). Another conserved region is the bromodomain, an approximately 110 amino acid long domain that is capable of binding to acetylated lysines (Dhalluin et al., 1999). Via this bromodomain, p300/CBP may not only bind to acetylated histones in nucleosomes, but also to acetylated DNA-binding transcription factors such as MyoD (Polesskaya et al., 2001). Apart from these structurally-defined modules that can be found in many other proteins, p300/CBP possess regions that are functionally defined as specific interaction domains for transcription factors (see Fig. 2).

p300/CBP themselves encompass transactivation domains at their N- and C-termini (Kwok et al., 1994; Janknecht and Nordheim, 1996b; Swope et al., 1996). When fused to the DNA-binding domain of the yeast transcription factor GAL4, these domains endow the resulting chimeric proteins with the ability to potently activate transcription from GAL4 DNA-binding sites, probably because both the N- and C-termini of p300/CBP are capable of interacting with TBP (Yuan et al., 1996) and thereby recruit the basal transcription machinery. Interestingly, the C-termini of p300/CBP are rich in the amino acid glutamine, which is often encountered in transactivation domains.

p300/CBP are histone acetyltransferases (HATs) (Bannister and Kouzarides, 1996; Ogryzko et al., 1996), and the respective catalytic portion of p300/CBP resides in the center of these molecules. Albeit originally found to acetylate histones H2A, H2B, H3 and H4, it has become obvious during the last years that p300/CBP modulate a variety of other proteins by acetylation, and should therefore no longer be regarded as HATs, but in a more general way as protein acetyltransferases.

Interaction partners of p300/CBP

Up to now, roughly 100 proteins have been

documented to associate with p300/CBP. These proteins interact with specific regions within p300/CBP (Fig. 2), and several ones can even bind to more than one region in p300/CBP, as exemplified for E1A (Kurokawa et al., 1998), Elk-1 (Janknecht and Nordheim, 1996a; Nissen et al., 2001), Ets-1 (Yang et al., 1998), YY1 (Austen et al., 1997), MyoD (Yuan et al., 1996; Polesskaya et al., 2001) and p53 (Gu et al., 1997; Grossman et al., 1998; Van Orden et al., 1999). The plethora of proteins binding to p300/CBP suggests that p300/CBP are general coactivators and may be as promiscuous as components of the basal transcription machinery. Since so many proteins interact with p300/CBP, it is not unsurprising to find that many physiological processes, including cell growth, cell division, cell differentiation, cell transformation, embryogenesis and apoptosis, are dependent on p300/CBP function. Whereas most often p300 and CBP can substitute for each other as interaction partners, a preference for, or exclusiveness of, one over the other coactivator may exist. For instance, the DRF1 and DRF2 transcription factors appear to interact with p300 but not CBP (Kitabayashi et al., 1995).

Interaction of proteins with p300/CBP can be constitutive, but may also be regulated. For instance, the cAMP-activated protein kinase A (PKA) phosphorylates the CREB transcription factor on serine 133, and this phosphorylation event is required for binding to p300/CBP (Chrivia et al., 1993). Members of the transforming growth factor-ß superfamily induce the phosphorylation of R-Smad proteins, which facilitates their binding to p300/CBP (Feng et al., 1998; Janknecht et al., 1998; Topper et al., 1998; Nakashima et al., 1999; Pearson et al., 1999). Similarly, ligand binding by nuclear hormone receptors is a prerequisite for efficient recruitment of the p300/CBP coactivators (Chakravarti et al., 1996; Hanstein et al., 1996; Kamei et al., 1996). Thus, a variety of different signaling pathways can induce the binding of transcription factors to p300/CBP.

On the other hand, p300/CBP are also targets of signaling pathways which induce posttranslational modifications in p300/CBP allowing them to bind more, or less, avidly to their interaction partners. For instance, epidermal growth factor and insulin induce the phosphorylation of CBP at serine 437 by protein kinase C (PKC), thereby enhancing its interaction with AP-1 or Pit-1 transcription factor complexes (Zanger et al., 2001). Interestingly, p300 has a glycine at the position homologous to serine 437 in CBP, thereby rendering it non-responsive to phosphorylation by PKC. Furthermore, phosphorylation of p300 on serine 89 (and probably also of CBP on the homologous serine residue 78) by the AMP-activated protein kinase represses its interaction with nuclear hormone receptors, but does not affect its interaction with other proteins such as p53 or E1A (Yang et al., 2001).

The ability of so many proteins to interact with p300/CBP links many transcription factors into a network, where competition for p300/CBP may account for the observation that unrelated factors inhibit each other without direct interference. This phenomenon is called squelching and relies on the fact that p300/CBP are in limited supply within the cell (Cahill et al., 1994; Kamei et al., 1996). In this vein, sequestration of p300/CBP by the adenoviral protein E1A is a means by which this viral protein can suppress many cellular

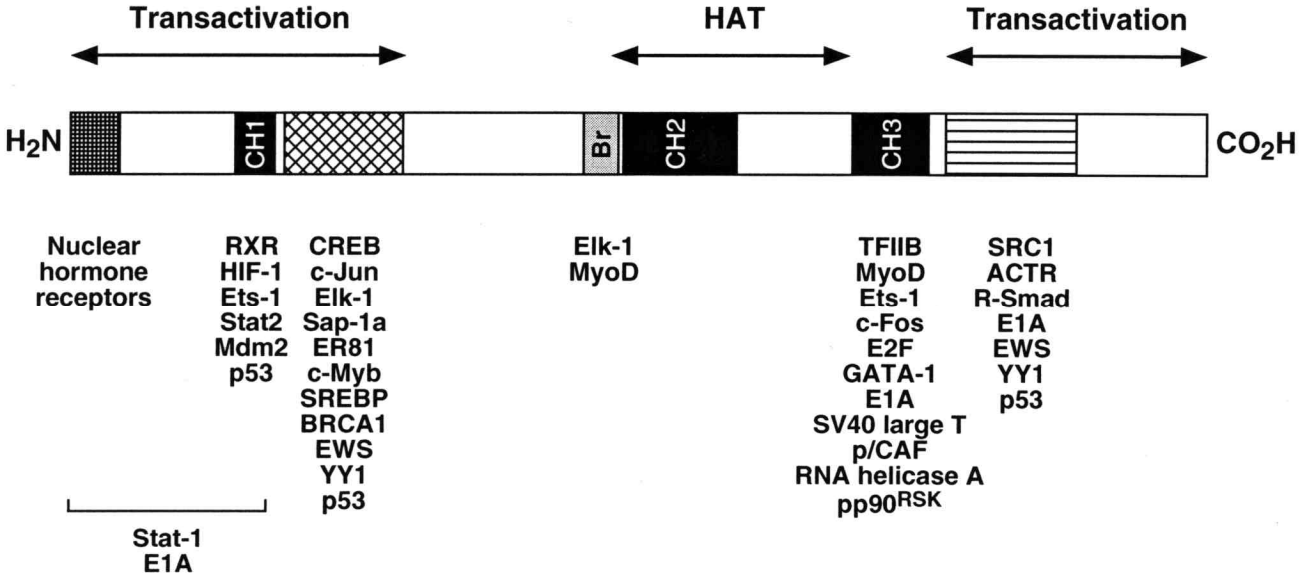

Fig. 2. Scheme of p300/CBP drawn to scale. Human p300 and CBP span 2414 and 2442 amino acids, respectively. CH1-3, cysteine/histidine-rich regions 1 to 3. Br: bromodomain capable of binding to acetylated lysine residues; HAT: the (histone) acetyltransferase activity in the center of p300/CBP. Shown is a selection of proteins that bind to the indicated protein-interaction domains within p300/CBP.

transcription factors and thereby contribute to cellular transformation (Arany et al., 1995; Lundblad et al., 1995).

As E1A, the simian virus 40 (SV40) large T protein and the polyomavirus large T protein are capable of interacting with p300/CBP and thereby obstruct the function of cellular transcription factors (Avantaggiati et al., 1996; Eckner et al., 1996; Nemethova and Wintersberger, 1999; Cho et al., 2001). Also, the human papillomavirus type 16 protein E6 interferes with p300/CBP function (Patel et al., 1999; Zimmermann et al., 1999), whereas the type 18 E2 protein activates viral transcription in conjunction with p300/CBP (Lee et al., 2000). Further examples of viral proteins suppressing transcription by competing with cellular transcription factors for binding to p300/CBP are the Kaposi's sarcoma-associated herpesvirus K8 protein or the human herpes virus 8 vIRF-1 protein (Hwang et al., 2001; Lin et al., 2001). On the other hand, the Epstein-Barr virus proteins EBNA2 and BRLF1 require interaction with p300/CBP for maximal transcriptional activation (Wang et al., 2000; Swenson et al., 2001). The human T-cell leukemia virus type 1 encoded Tax protein is a transcriptional activator and repressor, and Tax has been shown to activate gene transcription upon recruitment of p300/CBP in conjunction with the cellular transcription factor CREB, whereas it suppresses p53-dependent transcription, probably by preventing the recruitment of p300/CBP to p53 DNA-binding sites (Kwok et al., 1996; Suzuki et al., 1999). Furthermore, the human immunodeficiency virus-1 Tat protein binds to p300/CBP and recruits these coactivators to the chromosomally integrated viral long terminal repeats, thereby activating transcription of the integrated provirus (Benkirane et al., 1998; Hottiger and Nabel, 1998; Marzio et al., 1998). Collectively, these data point to ways how viruses can take over control of transcription: by competing with cellular transcription factors for binding to selective domains within p300/CBP, thereby shutting down transcription of cellular genes, and by cooperating with p300/CBP to stimulate viral gene transcription. As so many viruses exploit p300/CBP for their propagation, development of drugs that interfere with p300/CBP function may provide a cure to many viral infections.

Acetyltransferase activity of p300/CBP

p300/CBP both possess HAT activity and can acetylate nucleosomal proteins (Bannister and Kouzarides, 1996; Ogryzko et al., 1996). In general, acetylation of chromatin components such as nucleosomes is thought to decondense chromatin, make it more accessible for transcription factors and even remove nucleosomes from gene promoters and the transcribed region, thereby facilitating transcription initiation and elongation. p300/CBP can interact with nucleosomes via nucleosome assembly proteins, histone binding proteins and probably also via histones themselves (Shikama et al., 2000; Zhang et al., 2000; Manning et al., 2001), which puts p300/CBP into place for efficient acetylation of chromatin. Importantly, acetylation of H2A-H2B dimers by p300 mediates their transfer to nucleosome chaperones, which decreases chromatin folding allowing more efficient gene transcription (Ito et al., 2000). Since p300/CBP are associated with other HATs such as p/CAF or the steroid hormone receptor coactivators (Yang et al., 1996; Xu et al., 1999), recruitment of p300/CBP to nucleosomes may co-recruit a multitude of HATs with different specificities for chromatin components. Furthermore, p300/CBP may recruit other chromatin modifying enzymes, such as histone methyl transferases (Vandel and Trouche, 2001), but it remains to be studied how this affects gene transcription.

The HAT activity of p300/CBP is subject to regulation. The adenoviral protein E1A has been shown to inhibit their HAT activity (Chakravarti et al., 1999; Hamamori et al., 1999; Perissi et al., 1999), albeit one dissenting report has demonstrated an increase in HAT activity upon interaction with E1A (Ait-Si-Ali et al., 1998). Similarly, interaction with various transcription factors can modulate the acetyltransferase activity of p300/CBP, either enhancing or suppressing it (Hamamori et al., 1999; Chen et al., 2001; Lim et al., 2001; Shen et al., 2001; Soutoglou et al., 2001).

Apart from histones, many more proteins have been identified to be acetylated by p300/CBP. The first example was the tumor suppressor p53, whose acetylation by p300/CBP enhances its DNA-binding ability and thus promotes p53-dependent transcription (Gu and Roeder, 1997). Interestingly, stress-inducing agents such as hypoxia or actinomycin D and induction of DNA damage lead to the in vivo acetylation of p53 at the site that is in vitro acetylated by p300/CBP (Liu et al., 1999a; Ito et al., 2001), indicating that p53 function is indeed regulated by p300/CBP-mediated acetylation in the cell under circumstances when p53 activity is needed to slow cell growth and promote apoptosis.

GATA-1 and NF-E2, two transcription factors that are important for the terminal differentiation of gene expression in erythrocytes and megakaryocytes, are also acetylated by p300/CBP, resulting in enhanced DNA-binding activity (Boyes et al., 1998; Hung et al., 2001). Acetylation by p300/CBP may regulate a transcription factor's activity at many levels, as shown for the hepatocyte nuclear factor-4: acetylation increases DNA-binding and CBP-binding affinity as well as nuclear retention of this transcription factor (Soutoglou et al., 2000). Also, the proto-oncoprotein c-Myb, which is required for the proliferation of immature hematopoietic cells and for the development of T cells, is acetylated by p300/CBP, thereby gaining an enhanced affinity for p300/CBP which leads to increased target gene transcription (Sano and Ishii, 2001). The androgen receptor that is important for the induction of secondary sexual characteristics and for the dihydrotestosterone-induced proliferation of prostate cancer cells, MyoD that

is a key protein in muscle cell differentiation, and the human immunodeficiency virus-1 Tat protein are all stimulated in their ability to enhance gene transcription by p300/CBP-mediated acetylation (Ott et al., 1999; Fu et al., 2000; Polesskaya et al., 2000). Even the basal transcription factors TFIIE and TFIIF are acetylated by p300/CBP, but the functional significance of that remains to be elucidated (Imhof et al., 1997). Finally, the retinoblastoma tumor suppressor protein (pRb), whose phosphorylation by cell cycle-dependent protein kinases is pivotal for cell cycle progression, is acetylated by p300/CBP (Chan et al., 2001). The degree of pRb acetylation increases upon cell cycle induction of serum-starved cells or upon phorbol-ester-induced differentiation of U937 cells. Acetylation appears to decrease the ability of pRb to become phosphorylated, the consequence of which would be cell cycle arrest. However, pRb acetylation also promotes interaction with Mdm2, which in turn releases E2F out of the pRb/E2F complex, thus potentially enhancing cell cycle progression. How these antagonizing results of pRb acetylation integrate into an effect onto the cell cycle awaits more studies.

Regulation of p300/CBP function by direct phosphorylation

p300/CBP become hyperphosphorylated during the cell cycle or upon differentiation of F9 cells in response to retinoic acid (Yaciuk and Moran, 1991; Kitabayashi et al., 1995; Ait-Si-Ali et al., 1998). Consistently, the cell cycle-regulated cyclin E-Cdk2 complex associates with p300/CBP, is capable of phosphorylating CBP in vitro and thereby increases the HAT activity of CBP, and probably other cyclin-Cdk complexes can do so, too. Since in vivo phosphorylation of CBP and its HAT activity correlate with the in vivo activity of cyclin E-Cdk2, p300/CBP acetyltransferase activity may be upregulated at the G1/S boundary by cyclin E-Cdk2 and thereby contribute to the proper progression of the cell cycle (Banerjee et al., 1994; Perkins et al., 1997; Ait-Si-Ali et al., 1998).

The transactivation potential of p300/CBP can be increased by PKA or Ca^{2+}/calmodulin-dependent protein kinase IV, but aside from an in vitro demonstration of CBP phosphorylation by PKA, no proof of in vivo phosphorylation or of its relevance for p300/CBP activity has been provided (Kwok et al., 1994; Janknecht and Nordheim, 1996b; Chawla et al., 1998). On the other hand, phosphorlyation of p300 by PKC and the AMP-activated protein kinase at the same serine 89 residue has been convincingly demonstrated in vivo and in vitro, leading to a reduction of p300-dependent transactivation that is probably due to a reduction of interaction with specific transcription factors (Yuan and Gambee, 2000; Yang et al., 2001). Conversely, PKC phosphorylation at serine 437 in CBP appears to enhance it ability to be recruited by AP-1 and Pit-1 transcription factors, and thus to increase gene transcription (Zanger et al., 2001). Another report indicates that serine 1834 in p300 is phosphorylated by protein kinase B/Akt, and that phosphorylation at this site disrupts the interaction with the transcription factor C/EBPß. At the present time, one cannot distinguish whether this is due to a loss of affinity for C/EBPß or due to an increased affinity for another cellular factor that competes with C/EBPß for binding to the same region of p300 encompassing serine 1834 (Guo et al., 2001).

The p42/p44 MAPKs have been found to phosphorylate CBP in vitro and enhance the potency of its transactivation domains. Consistent with a function of MAPKs in p300/CBP regulation, they are associated with CBP and stimulate its HAT activity in vitro (Janknecht and Nordheim, 1996a; Liu et al., 1998, 1999b; Ait-Si-Ali et al., 1999). However, at present it remains unclear whether MAPKs indeed phosphorylate p300/CBP in vivo and thereby control p300/CBP function.

p300 and *Cbp* gene knock-outs

Homozygous $p300^{-/-}$ knock-out mice die early in embryogenesis. The reasons are poor cell proliferation, defects in heart development as well as defects in the process of neural tube closure. Due to the early death of these mice, one cannot observe the impact of *p300* deficiency on later events in embryogenesis, which may also be critically dependent on p300 function. Of note, a portion of heterozygous $p300^{+/-}$ mice already die in utero, suggesting that the normal dosage of p300 is limiting. Similarly, homozygous $Cbp^{-/-}$ knock-out mice are not viable, probably due to massive brain hemorrhage as a result of defective blood vessel formation, and die at around the same time in utero as *p300* knock-out mice. As $p300^{-/-}$ mice, $Cbp^{-/-}$ knock-out mice also display defective neural tube formation, suggesting that the CBP and p300 proteins are functionally interchangeable, and their extensive overlapping expression pattern during embryogenesis supports this notion. Consistently, double heterozygous $Cbp^{+/-}/p300^{+/-}$ mice are also embryonic lethal. However, one difference between *Cbp* and *p300* knock-out mice has been noted: abnormal heart formation occurs in $p300^{-/-}$ but not in $Cbp^{-/-}$ mice (Tanaka et al., 1997, 2000; Yao et al., 1998; Partanen et al., 1999). Altogether, these data suggest that both CBP and p300 are essential proteins for development, that at least three out of the four alleles of *Cbp* and *p300* must be active during embryogenesis, and that the CBP and p300 proteins are mostly, but not always functionally identical. In line with the latter notion, distinct roles of p300 and CBP during cell differentiation have been observed by using specific hammerhead ribozymes: F9 cells that were depleted of p300 did no longer differentiate in response to retinoic acid, whereas expression of a CBP-specific ribozyme had no effect (Kawasaki et al., 1998).

Another difference between CBP and p300 is noticeable in heterozygous knock-out mice. Only $Cbp^{+/-}$

mice display features of abnormal skeletal patterning that are reminiscent of Rubinstein-Taybi syndrome patients. In particular, abnormal development of frontal bones, the sternum, ribs and axial bones was observed in *Cbp*$^{+/-}$ mice (Tanaka et al., 1997; Cantani and Gagliesi, 1998). Importantly, analysis of Rubinstein-Taybi patients has revealed breakpoints and microdeletions at chromosome 16p13.3, coinciding with the locus of the *Cbp* gene (Petrij et al., 1995; Blough et al., 2000). However, a more severe and more penetrant Rubinstein-Taybi syndrome-like phenotype was displayed by mice in which one *Cbp* allele was modified to express a truncated CBP protein that may act in a dominant-negative fashion. These data suggest that not only *Cbp* haploinsufficiency, but also a dominant-negative CBP protein is necessary to elicit Rubinstein-Taybi syndrome, which is consistent with the autosomal dominant inheritance of this disease (Oike et al., 1999). However, no mouse model has up to now been capable of emulating the most frequent anomaly in Rubinstein-Taybi syndrome patients, the broad thumbs and broad big toes. This may be due to species differences between mice and humans, or indicate that additional genetic defects have to occur in Rubinstein-Taybi patients, for instance in genes juxtaposed to *Cbp* on chromosome 16 that become co-affected by 16p13.3 microdeletions.

Chromosomal translocations involving *p300* and *Cbp*

In contrast to the germline mutation of *Cbp* in Rubinstein-Taybi syndrome, somatic chromosomal alterations of the *Cbp* gene have been observed in hematological malignancies. The first reported case was a t(8;16)(p11;p13) translocation in the M4/M5 subtype of acute myeloid leukemia, in which the *Moz* (monocytic leukemia zinc finger protein) gene was fused to the *Cbp* gene. The resulting fusion protein consists at the N-terminus of a portion of the MOZ protein, including its zinc-fingers, acidic domain and HAT domain, and at the C-terminus of most of the CBP protein, including its HAT domain (Borrow et al., 1996; Giles et al., 1997). Thus, the resulting MOZ-CBP fusion proteins contain two HAT domains and may remodel chromatin very efficiently. Furthermore, a t(10;16)(q22;p13) translocation results in the generation of a MORF-CBP fusion protein. MORF (MOZ-related factor) is highly similar to MOZ, and the MORF-CBP fusion protein has a similar structure as MOZ-CBP, thus resulting in the same disease phenotype (Champagne et al., 1999; Panagopoulos et al., 2001).

The t(11;16)(q23;p13) translocation is characteristic of therapy-related leukemia or myelodysplasia and is thought to be a consequence of treatment with DNA topoisomerase II inhibitors. In these cases, a large portion of the MLL (mixed lineage leukemia) protein is fused N-terminally onto the CBP protein, which minimally contributes sequences C-terminal of its bromodomain to the MLL-CBP fusion proteins (Rowley et al., 1997; Satake et al., 1997; Sobulo et al., 1997; Taki et al., 1997). The AT-hook, which can bind to cruciform DNA, and the methyltransferase region of MLL are preserved in the MLL-CBP proteins. How the AT-hook and the methyltransferase activity contribute to the oncogenicity of the MLL-CBP protein remains to be determined, but those MLL features may, in conjunction with the HAT activity of the fused CBP portion, affect chromatin remodeling.

In contrast to *Cbp*, the *p300* gene appears to be less susceptible to chromosomal translocations. Accordingly, few cases of p300 translocations have been found, a t(11;22)(q23;q13) translocation leading to the MLL-p300 fusion and t(8;22)(p11;q13) translocations leading to MOZ-p300 fusions, which show a similar phenotype as the respective CBP fusion proteins (Ida et al., 1997; Chaffanet et al., 2000; Kitabayashi et al., 2001). All of the described chromosomal translocations involving *Cbp* and *p300* are reciprocal, so that two different fusion proteins are produced that might both contribute to disease development. However, MLL-CBP has been expressed in murine bone marrow by viral transduction, and the resulting phenotype was myelodysplastic-like syndrome that evolved into myeloid leukemia (Lavau et al., 2000). These data strongly indicate that the disease phenotype of t(11;16)(q23;p13) translocations is purely caused by the MLL-CBP fusion protein, and not the reciprocal CBP-MLL fusion that lacks any HAT activity. By inference, the same might hold true for all other translocations involving the *Cbp* and *p300* genes, and maybe the pivotal molecular defect is the dysregulation of p300/CBP HAT activity in the fusions with the MLL, MOZ and MORF proteins. If so, targeting the dysregulated HAT activity may be a potential avenue of therapy in the resulting leukemias.

p300 and CBP: tumor suppressor proteins?

p300 has been identified as a protein associated with the adenoviral E1A protein, which is a known agent capable of transforming cells. One hypothesis has been that E1A transformation of cells relies on the sequestration of the cellular p300 protein. Consistently, overexpression of p300 is capable of suppressing E1A-mediated transformation, the first indication that p300/CBP have tumor suppressing characteristics (Smits et al., 1996). Furthermore, somatic mutations have been found in the *p300* gene in colorectal, gastric, pancreatic and breast cancer, which were often accompanied by the loss of the second allele, a hallmark of a tumor suppressor gene (Muraoka et al., 1996; Gayther et al., 2000).

Analysis of heterozygous *Cbp*$^{+/-}$ mice has revealed that hematologic neoplasias arise in older animals. Importantly, loss of heterozygosity at the *Cbp* locus was found in some cases in the cancer cells. Correspondingly, Rubinstein-Taybi patients have an increased risk of acquiring tumors, albeit no loss of *Cbp* heterozygosity has yet been reported (Miller and

Rubinstein, 1995; Kung et al., 2000). Again, these data suggest a tumor-suppressing function for p300/CBP.

Finally, as cofactors for the known tumor suppressors p53 and BRCA1, p300/CBP could be required for the prevention of tumor formation. However, p300/CBP act also as cofactors for a variety of transcription factors that are regarded as proto-oncoproteins (e.g., c-Fos, c-Jun, c-Myb), in which case lack of p300/CBP should lead to a suppression of cell growth (Goodman and Smolik, 2000). Which interaction of p300/CBP is of more importance may depend on the cell type observed and the relative amount of p53 and BRCA1 versus c-Fos, c-Jun and c-Myb being expressed, and thus loss of the *p300* or *Cbp* genes may only in some cases lead to cancer.

Role of p300/CBP in neurodegenerative diseases

At least nine dominantly inherited neuro-degenerative diseases, Huntington's disease, dentatorubral pallidoluysian atrophy, spinal bulbar muscular atrophy and spinocerebellar ataxia type 1, 2, 3, 6, 7 and 12, are caused by the same molecular mechanism: expansion of a polyglutamine-encoding sequence. A microscopical hallmark of these diseases is the formation of inclusions, which are composed of aggregates of the disease-specific proteins and other polyglutamine-containing proteins. How this inclusion formation relates to the eventual induction of cell death in these neurodegenerative diseases is presently under study (Evert et al., 2000; Gusella and MacDonald, 2000).

Recent evidence suggests that sequestration of CBP may be one underlying cause of neurodegenerative diseases caused by expanded polyglutamine repeats (Kazantsev et al., 1999; McCampbell et al., 2000; Steffan et al., 2000; Nucifora et al., 2001). Expanded polyglutamine stretches in the huntingtin protein lead to intracellular aggregate formation and co-aggregation of CBP, but not of p300, in cell culture and Huntington's disease patient brains. This binding of CBP to huntingtin with an expanded polyglutamine repeat is dependent on the 18 residue polyglutamine repeat in the C-terminal transactivation domain of CBP, and may be mediated by a direct interaction between the two respective polyglutamine repeats. The longest polyglutamine repeat in p300 is only six residues long and thus probably too short to avidly bind other polyglutamine stretches, which would explain why p300 does not co-aggregate with huntingtin that has an expanded polyglutamine stretch. What are the consequences of CBP sequestration? Probably cell death, since overexpression of CBP, but not p300, could rescue polyglutamine-induced neuronal toxicity (Nucifora et al., 2001).

Another clue to how huntingtin with expanded polyglutamine repeats can lead to neurotoxicity came from a study investigating the HAT activity of CBP: the expanded polyglutamine repeat of huntingtin can bind more avidly and thus suppress more efficiently the HAT domain of CBP. Interestingly, the HAT activities of p300 and the p300/CBP-associated p/CAF protein are also significantly suppressed by the expanded polyglutamine repeat of huntingtin. Consistently, huntingtin expression reduces histone acetylation in vivo, and importantly, raising histone acetylation by administration of histone deacetylase inhibitors can arrest polyglutamine-dependent neurodegeneration in a Drosophila model (Steffan et al., 2001). Future clinical studies with histone deacetylase inhibitors should prove their value as a treatment option in polyglutamine-caused neurodegenerative diseases. On the other hand, drugs that increase the residual HAT activity of p300/CBP may also be a treatment option, but such drugs have not yet been developed.

Concluding remarks

p300/CBP are ubiquitous, versatile transcriptional coactivators that are essential for development and many other physiological processes. However, p300/CBP may not only be involved in transcriptional events, but also contribute to DNA repair by remodeling of chromatin at sites of DNA lesions and/or recruitment of the proliferating cell nuclear antigen, thereby allowing the latter to exert its many functions in DNA repair synthesis (Hasan et al., 2001). p300/CBP might also be involved in RNA splicing, since it interacts with the RNA-binding protein EWS (Rossow and Janknecht, 2001). Clearly, p300/CBP can be oncogenic when fused to other chromatin modifying proteins such as MOZ, MORF and MLL, but on the other hand a growing body of evidence points to their genuine role as tumor suppressors.

What more will be discovered about p300/CBP in the future? One aspect of research should focus on the generation of conditional knock-outs for *p300* and/or *Cbp*, which will allow to discern the functions of these coactivators in specific tissues and beyond mid-gestation when constitutive *p300* or *Cbp* knock-out mice die. Surely, one will witness the identification of many more p300/CBP interaction partners, and thus learn more about potential mechanisms how p300/CBP affect physiological processes. But most exciting may be the unraveling of novel aspects of p300/CBP function, especially in human diseases, and the development of therapies targeting p300/CBP in viral infections, leukemias or neurodegenerative diseases.

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