Oncogene (2004) 23, 4225–4231

www.nature.com/onc

p300/CBP and cancer

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p300 and cyclic AMP response element-binding protein (CBP) are adenoviral E1A-binding proteins involved in multiple cellular processes, and function as transcriptional co-factors and histone acetyltransferases. Germline mutation of CBP results in Rubinstein–Taybi syndrome, which is characterized by an increased predisposition to childhood malignancies. Furthermore, somatic mutations of p300 and CBP occur in a number of malignancies. Chromosome translocations target CBP and, less commonly, p300 in acute myeloid leukemia and treatment-related hematological disorders. p300 mutations in solid tumors result in truncated p300 protein products or amino-acid substitutions in critical protein domains, and these are often associated with inactivation of the second allele. A mouse model confirms that p300 and CBP function as suppressors of hematological tumor formation. The involvement of these proteins in critical tumorigenic pathways (including TGF-β, p53 and Rb) provides a mechanistic route as to how their inactivation could result in cancer.
Oncogene (2004) **23,** 4225–4231. doi:10.1038/sj.onc.1207118

Keywords: p300; CBP; mutations; translocations

Introduction

p300 was originally identified using protein-interaction assays with the adenoviral E1A oncoprotein (Eckner *et al*., 1994). p300 has been implicated in a number of diverse biological functions including proliferation, cell cycle regulation, apoptosis, differentiation and DNA damage response (Giles *et al*., 1998; Giordano and Avantaggiati, 1999; Goodman and Smolik, 2000; Chan and La Thangue, 2001). p300 is highly homologous to the cyclic AMP response element-binding (CREB) protein (CBP), with 63% homology at the amino-acid level. The two proteins have a number of common roles in physiological processes, although it is increasingly clear that they serve several distinct, non-overlapping functions. Both p300 and CBP are evolutionarily conserved in metazoans as diverse as mouse, *Xenopus*, *Drosophila* and *C. elegans*, although in lower organisms there is a single orthologue.

p300/CBP function primarily as transcription co-factors for a number of nuclear proteins. These include known oncoproteins (such as myb, jun, fos), transforming viral proteins (such as E1A, E6 and large T antigen) and tumor-suppressor proteins (such as p53, E2F, Rb, Smads, RUNX and BRCA1) (Eckner *et al*., 1994; Bannister and Kouzarides, 1995; Bannister *et al*., 1995; Avantaggiati *et al*., 1997; Lill *et al*., 1997; Pouponnot *et al*., 1998; Patel *et al*., 1999; Ghosh *et al*., 2000; Martinez-Balbas *et al*., 2000; Marzio *et al*., 2000; Pao *et al*., 2000; Tomita *et al*., 2000; Chan *et al*., 2001). Transcriptional coactivation is mediated by p300/CBP acting as a bridge linking DNA-binding transcription factors to the basal transcriptional machinery. In addition, the surface of these molecules works as a scaffold for the nucleation of various transcription factors involved in complex cellular responses. The classical model of p300/CBP as a scaffold is based on experiments performed on the β-interferon gene promoter in response to viral infection (Merika *et al*., 1998; Munshi *et al*., 1998). Upon stimulation, the β-interferon enhanceosome is assembled on the surface of the p300 molecule, bringing together transcription factors such as NF-κB, IRF1, ATF2/c-Jun and the architectural protein HMG I(Y) to the β-interferon gene promoter. The role of p300 in this response is critical, as it brings about the assembly of specific nuclear factors and the RNA polymerase holoenzyme to execute a rapid, but brief, transcriptional activation of the β-interferon gene.

In 1996, two independent groups confirmed that p300 and CBP function as histone acetyltransferases (HATs) (Bannister and Kouzarides, 1996; Ogryzko *et al*., 1996). Unlike other HATs, which have limited substrate specificity for histones, p300 and CBP are capable of acetylating all the four histones *in vitro* and probably *in vivo*. Acetylation of specific lysine residues on histone tails is believed to neutralize the negative charge, reducing the tight interaction between histones and the DNA molecule. Histone acetylation has long been associated with genes that are actively transcribed (Allfrey *et al*., 1964). Therefore, p300 and CBP appear to couple transcription factor recognition to chromatin remodelling. It is now known that the coordination of gene transcription is controlled by a variety of histone modifications including acetylation, phosphorylation, methylation and ubiquitination. The complex combination of these modifications constitutes the 'histone code', which mediates the activation and repression of specific gene transcription (Strahl and Allis, 2000). p300 and CBP are also capable of acetylating a number of non-histone proteins, including p53, p73, Rb, E2F, myb, myoD, HMG(I)Y, GATA1 and α-importin

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(Gu and Roeder, 1997; Boyes *et al*., 1998; Munshi *et al*., 1998; Sakaguchi *et al*., 1998; Bannister *et al*., 2000; Martinez-Balbas *et al*., 2000; Marzio *et al*., 2000; Tomita *et al*., 2000; Chan *et al*., 2001; Polesskaya and Harel-Bellan, 2001; Costanzo *et al*., 2002). This has led to the suggestion that acetylation of nonhistone proteins is an important post-translation modification, analogous to phosphorylation (Kouzarides, 2000). Like phosphorylation, acetylation of proteins can affect a number of different pathways. Acetylation of sequence-specific DNA-binding nuclear proteins such as p53, p73, Rb and E2F (on lysine residues adjacent to DNA-binding domains) augments promoter binding, resulting in activation of transcriptional activity. In contrast, acetylation of HMG(I)Y on lysine residues within the DNA-binding domain reduces transcriptional activity. Acetylation also affects protein–protein interactions as in the case of Rb and mdm2, and may be involved in nuclear import and microtubule assembly (Takemura *et al*., 1992).

p300 and CBP have been implicated in embryonic development and cancer. The role of p300 as a putative tumor-suppressor gene has been suspected since its identification as an E1A-binding protein. In this review, we summarize the evidence for the potential role of p300 and CBP in cancer. While the published data often fail to distinguish between p300 and CBP, analysis of chromosome translocations in hematological malignancies and mutations in solid tumors suggest a fundamental difference in the involvement of these homologues in cancer. Furthermore, a number of experiments have also suggested differences in mechanisms by which the two proteins may affect tumor formation.

Germline mutations: Rubinstein–Taybi syndrome

Rubinstein–Taybi syndrome (RTS) is a developmental disorder caused by heterozygous germline mutations (point mutations, translocations or deletions) of the CBP gene (Petrij *et al*., 1995, 2000; Rubinstein, 1990). RTS is characterized by broad thumbs, cranio-facial and cardiac abnormalities, as well as mental retardation. Patients with RTS have an increased predisposition to cancer, usually childhood tumors of neural crest origin (an approximate incidence of 5%) (Miller and Rubinstein, 1995). However, it has not been determined if the remaining CBP allele is somatically mutated/inactivated in these tumors. To date, no syndrome involving the germline mutation of the p300 gene has been described.

Somatic mutations: p300 and CBP translocations in leukemia/lymphoma

The earliest observations linking p300 and CBP to cancer were studies in leukemias, where chromosome translocations disrupt the CBP gene. The first to be characterized was the t(8,16)(p11,p13) translocation associated with the M4/M5 subtype of acute myeloid leukemia (AML) (Borrow *et al*., 1996; Giles *et al*., 1997a; Panagopoulos *et al*., 2001). This translocation fuses the gene encoding the monocytic leukemia zinc-finger protein (MOZ) with the amino terminus of CBP. The t(8,16) translocation is rare, accounting for only four in 1000 patients with AML. An even rarer variant has been described, t(8,22)(p11,q13), which fuses MOZ to p300 (Lai *et al*., 1985; Chaffanet *et al*., 2000; Kitabayashi *et al*., 2001b). MLL-CBP and MLL-p300 translocations (MLL-mixed lineage leukemia) have also been described in treatment-related hematological disorders (Ida *et al*., 1997; Rowley *et al*., 1997; Satake *et al*., 1997; Sobulo *et al*., 1997; Taki *et al*., 1997). While the MOZ-CBP translocation may result in activation of the HAT domain in the fusion protein, loss of the amino terminus, which is a common event in all known translocations, may be important for cellular transformation (Champagne *et al*., 2001; Kitabayashi *et al*., 2001a). Chromosomal rearrangements involve CBP more commonly than p300. As most of the CBP rearrangements target the same 13 kb genomic interval, it is thought that the presence of an unstable genomic element in this region may account for the higher frequency (Giles *et al*., 1997b).

Somatic mutations: p300 and CBP in solid tumors

In solid tumors, loss of heterozygosity (LOH) studies have identified the long arm of chromosome 22 as a frequent target of allelic imbalance in a variety of malignancies including colorectal, breast, ovarian, hepatocellular and oral carcinomas, meningiomas, schwannomas and phaeochromocytomas (Chen *et al*., 1992; Shin *et al*., 1993; Takahashi *et al*., 1993; Englefield *et al*., 1994; Ruttledge *et al*., 1994; Twist *et al*., 1994; Bryan *et al*., 1996; Duriez *et al*., 1997; Allione *et al*., 1998; Miyakawa *et al*., 1998). Inactivation of the NF2 gene on 22q12 probably accounts for the allelic loss seen in tumors of neural crest origin. However, the search for a tumor-suppressor gene on 22q in the colon, breast, ovarian and hepatocellular carcinomas prompted mutational analyses of other genes in the region. The first of these studies on the p300 gene (located on 22q13) was performed on 27 primary colon adenocarcinomas and two primary gastric adenocarcinomas (Muraoka *et al*., 1996). Two missense point mutations were uncovered, one in each tumor type. These somatic mutations resulted in amino-acid substitutions at conserved residues in critical domains on the p300 protein (colorectal carcinoma – HAT domain, and gastric carcinoma – cysteine–histidine-rich domain 2), and were both associated with loss of the wild-type allele. The analysis was extended in our laboratory to include a total of 222 cancer samples (Gayther *et al*., 2000; Ozdag *et al*., 2002). Truncating mutations were seen in six out of 107 (5.6%) cell lines and two out of 115 (1.7%) primary tumors. The resultant truncated proteins had loss of important domains, and were associated with loss or silencing of the second allele, therefore suggestive of a classical tumor-suppressor 'two-hit' inactivation. Further mutations in cell lines and primary tumor samples have been described, but appear to be uncommon (Ohshima *et al*.,

2001; Bryan *et al*., 2002; Suganuma *et al*., 2002). The data on the frequency of mutations are summarized in Table 1. Table 2 contains a description of all mutations described to date.

CBP mutations are even rarer: only two heterozygous truncations were detected in cell lines, and no other mutations seen in 63 cancer cell lines and 116 primary tumors (Ozdag *et al*., 2002).

A recent study was carried out to identify LOH at the 22q13 p300 locus and 16p13 CBP locus (Tillinghast *et al*., 2003). Screening a panel of 103 cell lines showed LOH of 51% at the p300 locus and 35% at the CBP locus. Concordant loss at both loci occurred in 19% of cell lines, but this was not a statistically significant event. Expression levels of p300 and CBP were not determined, so these results suggest that haploinsufficiency resulting from loss of one paralogue is sufficient for tumor progression. Western blots of whole-cell lysates (using p300 N-terminal antibody) and mutational analyses of limited regions were performed in selected samples. However, these analyses failed to identify the previously described p300 mutations in cell lines HCT15, HT29, OVCAR8 and MDA-435. We decided not to include this study in the tables, which are only based on analyses where the whole gene was screened.

A cell line with mutation of both p300 alleles

HCT116 is a near-diploid colorectal carcinoma cell line in which we initially described a heterozygous truncating mutation of p300 at the DNA level on exon 31 (nucleotide 6294 *delA*), associated with no expression of the second allele at the RNA level. The mutation results in the monoallelic expression of a p300 protein truncated downstream of the HAT domain. Subsequently, a second frameshift mutation on exon 27 (nucleotide 5601 *delA*) was described in the DNA of this cell line (Bryan *et al*., 2002). This mutation would be predicted to truncate the protein within the HAT domain. We have recently confirmed that only the allele with a mutation on exon 31 is expressed, while the second mutation on exon 27 occurs in the second allele and is not expressed. These results suggest that RNA transcribed from the allele with the exon 27 mutation is degraded by nonsense-mediated mRNA degradation (NMRD). This is a known phenomenon in cells with biallelic truncating mutations at different sites, where transcripts from the allele with a mutation upstream (i.e. 5′) are preferentially degraded (Cao and Parker, 2003). The interest in this cell line resides in that the truncated p300 has intact acetyltransferase activity seen in *in vitro* histone acetylation assays and normal p53 acetylation in response to DNA damage (Sakaguchi *et al*., 1998; Gayther *et al*., 2000).

There are other cell lines with biallelic p300 mutations at the DNA level. In HOC313 (oral squamous cell carcinoma cell line), mutations were detected on nucleotides 6540 and 6822. Only the allele with a mutation in nucleotide 6822 (i.e. the 3′ mutation) is expressed (Suganuma *et al*., 2002). In another example, LIM2405 (colorectal carcinoma cell line), frameshift mutations were identified in nucleotides 3929 and 5601. Both alleles are not expressed in this cell line (Bryan *et al*., 2002).

Mutations of other HATs – p/CAF

Mutational analyses of p/CAF (p300/CBP-associated factor), a HAT homologous to Gcn5, have also been performed (Nishimori *et al*., 2000; Ozdag *et al*., 2002). Only missense variants were identified, with no truncating or loss of function mutations.

Table 1 Mutational analyses of p300 in solid tumors

Tissue of origin	*Mutations/samples analysed*	*Mutation type*	*Reference*
Primary tissue			
Colorectal	3/80	1 non (trunc) 2 *mis*	Muraoka (1996), Gayther (2000), Ozdag (2002), Bryan (2002) Gayther (2000),Ozdag (2002), Bryan (2002)
Breast	2/70	1 *fs* (*trunc*)	
Ovarian	0/156	1 *ifi*	
Gastric	1/2	*1 mis*	Muraoka (1996)
Cell lines			
Colorectal	6/35	3 *fs* (*trunc*) 3 *non* (*trunc*)	Gayther (2000), Ozdag (2002), Bryan (2002)
Breast	3/39	1 *fs* (*trunc*) 1 *spl* (*trunc*) 1 *mis*	
Ovarian	1/49	*1 fs* (*trunc*)	
Pancreatic	2/11	1 *fs* (*trunc*) 1 *mis*	Gayther (2000), Ozdag (2002), Ohshima (2001), Suganuma (2002)
Others	2/20	1 *ifd* (trunc) 1 *fs* (*trunc*)	

Mutation types: *fs* – frameshift, *non* – nonsense, *mis* – missense, *ifd* – in-frame deletion, *ifi* – in-frame insertion, *spl* – splice-site alteration resulting in frameshift, (*trunc*) – mutation that results in a truncated p300 protein

Table 2 p300 mutations described to date

Sample		*Mutation and codon change*		*Domain*	*Second allele*	*Reference*
			Truncating mutations			
Primary tumors						
Breast ca	*fs*	6294delA	—	CH3	Hemi	Gayther (2000)
Breast ca	*ifi*	5426ins18	6 aa insertion in exon 26	HAT	?	
Colorectal ca	*non*	2837C>T	R580X	KIX	Loss	
Cell lines						
Colorectal ca						
HCT116	*fs*	5601delA		HAT	Allele 1 (not expressed)	Gayther (2000), Ozdag (2002), Bryan (2002)
	fs	6294delA		CH3	Allele 2	
DLD1	*non*	4239A>G	E1014X	CH2	Wt	
HCT15	*non*	4239A>G	E1014X	CH2	Loss	
LIM2412	*non*	1455C>T	R86X	N-term	Wt	
LIM2405	*fs*	3979insC		CH2	Allele 1 (not expressed)	
	fs	5601insA		HAT	Allele 2 (not expressed)	
HT29	*fs*	5601insA		HAT	Wt	
Breast ca						
MATU	*spl*	6260+2T>A 6260ins28		CH3	Allele 1	Gayther (2000)
	ifd	4790del138 delete exon 20, 21		HAT	Allele 2	
VP229	*fs*	6294delA		CH3	Hemi	
Pancreatic ca						
Patu8988t	*fs*	4342del448		Bromo	Homo	Gayther (2000)
Ovarian ca						
OVCAR8	*fs*	6387delT		C-term	Wt	Ozdag (2001)
Oral squamous cell ca						
HOC313	*non*	6822C>T	Q1874X	C-term	Allele 1	Suganuma (2002)
	mis	6540C>G	P1780A	C-term	Allele 2 (not expressed)	
Cervical ca						
SiHa	*ifd*	4020del684 delete exon 15-18	Delete aa 940-1167	Bromo (deleted)	Homo	Ohshima (2001)
			Missense mutations			
Primary tumors						
Colorectal ca	*mis*	6240C>T	R1680C	CH3	Loss	Muraoka (1996)
Gastric ca	*mis*	5397G>T	N1399Y	HAT	Loss	
Colorectal ca	*mis*	7861C>A	P2221Q	C-term	Loss	Gayther (2000)
Cell lines						
Breast ca						
MDA435S	*mis*	3679T>C	L827P	CH2	Hemi	Gayther (2000)
	mis	4237A>G	E1013G	Bromo	Hemi	
Pancreatic						
Patu8902	*mis*	6148C>A	S1650Y	CH3	Wt	Gayther (2000)

Mutation types: *fs* – frameshift, *non* – nonsense, *mis* – missense, *ifd* – in-frame deletion, *ifi* – in-frame insertion, *spl* – splice-site alteration resulting in frameshift. p300 domains: CH1, CH2, CH3 – cysteine–histidine-rich domains 1, 2 and 3, respectively; KIX – kinase-inducible binding domain; bromo – bromodomain, N-term, C-term – N and C terminals, respectively, HAT – histone acetyltransferase domain. Second allele status: hemi – hemizygous (only one expressed transcript), loss – of second allele, ? – unknown, wt – wild type, allele 1, allele 2 – different alleles, homo – homozygous mutation

p300 and CBP – tumor-suppressor genes?

Since mutations are uncommon, doubts remain that p300/CBP function as classical tumor-suppressor genes. Transgenic mouse models can be important in establishing the pathogenic role of specific gene inactivation in cancer. CBP and p300 knockouts (homozygous null, −/−) are early embryonic lethal (Yao *et al*., 1998; Oike

et al., 1999a, b). Double heterozygotes and a significant fraction of p300 heterozygotes also do not survive embryogenesis, confirming that the presence of one homologue is insufficient to compensate for loss of the other. CBP heterozygotes developed multiple phenotypic abnormalities (similar to RTS), hematopoeitic failure and, eventually, hematological malignancies (Oike *et al*., 1999a; Kung *et al*., 2000). Importantly, in these malignancies, there was somatic inactivation of the second CBP allele, confirming that, at least in the mouse, CBP functions as a classical tumor-suppressor gene. The effect of complete inactivation of p300 and CBP has recently been assessed using chimeric mice (Rebel *et al*., 2002). Embryonic stem cells null for p300 and CBP were generated and injected into blastocysts of different mice strains to obtain p300 and CBP null chimeras. Both CBP and p300 chimeras developed hematological malignancies (thymic lymphoma and histiocytic sarcomas, respectively). These tumors were only composed of cells null for the respective protein, confirming that both CBP and p300 appear to play a role in suppressing hematologic tumor development.

As p300 was identified as an adenoviral E1A-binding protein, experiments on the transforming ability of E1A revealed that interaction with p300 is required to induce S-phase entry, override contact inhibition and block major differentiation pathways (Eckner *et al*., 1994; Smits *et al*., 1996; Yang *et al*., 1996). Furthermore, E1A proteins from oncogenic and non-oncogenic adenoviruses differ in their mechanisms of binding p300 (Lipinski *et al*., 1999). Both the papillomavirus E6 protein and SV40 large T antigen require interaction with p300 for cellullar transformation and dysregulation of the p53 pathway (Eckner *et al*., 1996; Patel *et al*., 1999; Zimmermann *et al*., 1999).

p300 is a key cofactor in the proper functioning of other tumor-suppressor proteins. Critical pathways such as the TGF-β, p53 and Rb-E2F pathways require p300 cofactor activation to mediate the transcription of target genes.

Smads and RUNX cooperate with p300 to trigger transcription of target genes in response to TGF-β activation and signalling (Pouponnot *et al*., 1998; Ghosh *et al*., 2000). The involvement of this pathway is not only intriguing but also highlight the possible mechanisms to explain the tumor-suppressor role of p300. TGF-β, Smad2, Smad 4 and RUNX have all been shown to function as suppressors of tumor formation in mouse knockout models, and appear to be inactivated in a number of malignancies (reviewed in Ito and Miyazono, 2003). The role of p300 in the TGF-β pathway has been established in a recent study (Suganuma *et al*., 2002). Transfection of full-length, wild-type p300 in cell lines with truncating p300 mutations resulted in reduction of proliferative capacity in these cells. Growth suppression was achieved by activation of TGF-β-dependent transcriptional activity, suggesting that deregulation of this signalling pathway may present a mechanism by which p300 mediates its tumor-suppressing ability. Transfection of CBP in the same cell lines was unable to suppress growth under identical conditions, suggesting the specificity of the p300 effect.

p300/CBP modulate the p53 pathway at multiple levels (reviewed in Grossman, 2001). p300 contributes to maintaining p53 stability by regulating its ubiquitination and degradation, through both mdm2-dependent and -independent mechanisms (Grossman *et al*., 1998, 2003; Kawai *et al*., 2001). After DNA damage, p53 is activated by phosphorylation by various kinases and acetylation at specific amino-acid residues by p300/CBP (Sakaguchi *et al*., 1998). p53 acetylation is thought to promote target gene activation by increasing the stability of the p53–p300–DNA complex (Gu and Roeder, 1997; Dornan *et al*., 2003). Furthermore, p300 is required for p53-mediated transactivation of target genes through its coactivator function and acetylation of target gene histones (Avantaggiati *et al*., 1997; Lill *et al*., 1997; Barlev *et al*., 2001; Espinosa and Emerson, 2001). Loss of p300 could disrupt p53 activation, stability, transactivation of target genes and alter the cell fate in response to p53 activation. In fact, p300 knockdown by hammerhead ribozymes inhibits apoptosis, probably by disrupting the p53-mediated response to DNA damage (Yuan *et al*., 1999a, b).

Despite all the evidence presented above, results from a number of experiments appear to question the tumor-suppressor function of p300 and CBP. For example, fibroblasts obtained from p300 and CBP null embryos have significant proliferation defects, and cannot be maintained in culture as cells uniformly progress to senescence (Yao *et al*., 1998; Oike *et al*., 1999a, b). Similarly, when p300 and CBP are knocked down using hammerhead ribozymes, resultant cells have markedly reduced proliferative capacity (Yuan *et al*., 1999a). Experiments on human melanocyte cultures suggest that reduction of p300 levels precede the activation of senescent checkpoints (Bandyopadhyay *et al*., 2002). p300 and CBP are also required for maintaining cells in cycle, as microinjecting antibodies against p300/CBP inhibit the S-phase entry and result in G1/S arrest (Ait-Si-Ali *et al*., 2000).

Conclusion

On balance, the evidence appears to weigh in favor of both p300 and CBP playing a role in tumorigenesis. p300 truncating mutations in solid tumors are rare, but do occur, and are associated with loss of the second allele. In hematological malignancies, translocations more commonly target CBP, probably due to the presence of an unstable genomic element within the 5′ end of the gene. Recent data from our laboratory show that a proportion of breast and colorectal carcinomas express p300 at extremely low levels (H Ozdag and C Caldas – unpublished observations). The significance of these findings is supported by its tissue specificity, as bladder, renal and ovarian tumors do not appear to have significant expression abnormalities. Moreover, it is clear that both p300 and CBP function as

tumor suppressors in mice, where deficiency results in the development of hematological malignancies. The role of p300 in pathways critical in tumorigenesis (p53, Rb-E2F or TGF-β) could be a mechanism by which p300 contributes to cancer formation.

Acknowledgements

NGI was a recipient of the NMRC (Singapore) Medical Research Fellowship. HO was funded by a European Union Grant. Work in the Caldas laboratory is supported by Cancer Research UK.

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