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REVIEW

Transcriptional/epigenetic regulator CBP/p300 in tumorigenesis: structural and functional versatility in target recognition

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Abstract In eukaryotic cells, gene transcription is regulated by sequence-specific DNA-binding transcription factors that recognize promoter and enhancer elements near the transcriptional start site. Some coactivators promote transcription by connecting transcription factors to the basal transcriptional machinery. The highly conserved coactivators CREB-binding protein (CBP) and its paralog, E1A-binding protein (p300), each have four separate transactivation domains (TADs) that interact with the TADs of a number of DNA-binding transcription activators as well as general transcription factors (GTFs), thus mediating recruitment of basal transcription machinery to the promoter. Most promoters comprise multiple activator-binding sites, and many activators contain tandem TADs, thus multivalent interactions may stabilize CBP/p300 at the promoter, and intrinsically disordered regions in CBP/p300 and many activators may confer adaptability to these multivalent complexes. CBP/p300 contains a catalytic histone acetyltransferase (HAT) domain, which remodels chromatin to 'relax' its superstructure and enables transcription of proximal genes. The HAT activity of CBP/p300 also acetylates some transcription factors (e.g., p53), hence modulating the function of key transcriptional regulators. Through these numerous interactions, CBP/p300 has been implicated in complex physiological and pathological processes, and, in response to different signals, can drive cells towards proliferation or apoptosis. Dysregulation of the transcriptional and epigenetic functions of CBP/p300 is associated with leukemia and other types of cancer, thus it has been recognized as a potential anti-cancer drug target. In this review, we focus on recent exciting findings in the structural mechanisms of CBP/p300 involving multivalent and dynamic interactions with binding partners, which may pave new avenues for anti-cancer drug development.

Keywords Transcriptional coactivator · Transcription factors · CBP/p300 · Protein–protein interaction · Histone acetyltransferase (HAT) · Cancer

Introduction

Eukaryotic gene activation requires the concerted function of transcription factors and coactivators [1]. Transcription activators bind cognate sites in the promoter and enhancers of target genes and stimulate transcription by bringing the basal (general) transcription machinery, which includes the general transcription factors (GTFs) (TFIIA, TFIIB, TFIID, TFIIE, TFIIF, and TFIIH) and RNA Pol II itself [2], to the transcription initiation site [3]. Although some activators can directly interact with the GTFs (e.g., TFIID) [4–6], in most cases, additional proteins or multi-protein complexes, called coactivators, are required to facilitate this process [7–9]. Initially, coactivators were viewed as adaptor proteins that connect the sequence-specific transcription factors to the basal transcription machinery [7, 8]; however, it was later appreciated that some coactivators have additional

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functions. In eukaryotic cells, DNA wraps around histone octamers to assemble nucleosomes, which are further packaged into condensed euchromatin that is inaccessible for transcription [10]. Another class of transcriptional coactivators was found to possess chromatin-remodeling or modification activity, which opens the chromatin structure to allow effective gene transcription [11]. Another level of transcriptional regulation is achieved through the modulation of the expression and activation of the coactivators [12].

CBP and its paralog p300 (also called EP300) are transcriptional coactivators for many important transcription factors, and perform both the functions discussed above: bridging of DNA-binding and general transcription factors (Fig. 1a), and relaxation of chromatin through its intrinsic

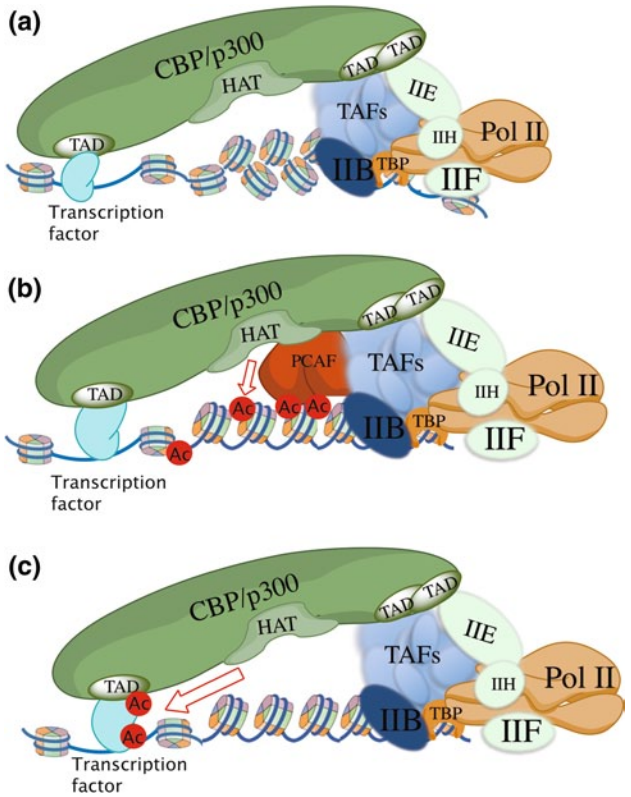


Fig. 1 Functional mechanisms of transcriptional activation by CBP/p300. CBP/p300 promotes transcriptional activity by recruiting transcriptional machinery to the promoter, and by modifying chromatin structure to facilitate transcription. **a** CBP/p300 functions as a "bridge", linking the DNA-bound transcription factors (activators) to basal transcription machinery through direct interactions with TFIID (comprised of TATA-binding protein (TBP) and 13 TBP-associated factors (TAFs)), TFIIB, and RNA polymerase II (RNA Pol II), thus promoting pre-initiation complex (PIC) assembly. **b** CBP/p300 acetylates histones through its histone acetyltransferase (HAT) domain, resulting in chromatin remodeling and relaxation of chromatin structure to enable transcription. CBP/p300 also recruits the coactivators PCAF and GCN5, which also possess HAT activity. **c** CBP/p300 HAT activity also acetylates certain transcription factors, modulating their activities positively or negatively

histone acetyltransferase (HAT) activity [13–15] (Fig. 1b). In addition, CBP/p300 also acetylates some transcription factors, thus modulating their activity (Fig. 1c). In some specific circumstances, CBP and p300 play distinct roles; however, their functions are largely redundant [16]. Because of their structural similarity and functional redundancy, CBP and p300 are often referred to collectively as CBP/p300.

p300 was first discovered on the basis of its interaction with adenoviral protein E1A, and the chromosomal location of p300 gene was subsequently mapped to 22q13 [17, 18]. Shortly thereafter, CBP was independently identified as the binding partner and coactivator of cAMP response element-binding (CREB) protein, and the CBP gene was localized to chromosomal region 16p13.3 [19–21]. These two proteins share ~75 % sequence similarity and ~63 % identity. Most known functional domains of CBP/p300 are found within the highly conserved regions, including four recognized transactivation domains (TADs): (1) the Cysteine–Histidine-rich region 1 (CH1) that encompasses the transcriptional adapter zinc finger 1 (TAZ1) domain [22, 23], (2) the CREB-interacting KIX domain [24], (3) another Cysteine–Histidine-rich region (CH3) containing the transcriptional adapter zinc finger 2 (TAZ2) domain and a ZZ-type zinc finger domain [23, 25], and (4) the nuclear receptor co-activator binding domain (NCBD), which is also called interferon-binding domain (IBiD) [26, 27]. These TADs mediate the protein–protein interactions with DNA-binding transcription factors and basal transcription machinery, as well as other coactivators. CBP/p300 also contains a catalytic HAT domain that acetylates histones and other proteins, and an adjacent Bromo domain that recognizes acetylated histone tails [28]. Flanking the catalytic core, there is another Cysteine–Histidine-rich region (CH2), comprised of the plant homeodomain (PHD) (Fig. 2). CBP/p300 interacts with a wide spectrum of transcription factors through its four TADs [29]. CBP/p300 association factors include pro-proliferative proteins and oncoproteins: c-Myc [30], c-Myb [31], CREB [19], c-Jun [32], and c-Fos [33]; transforming viral proteins: E1A [17, 18], and E6 [34]; as well as tumor suppressors and pro-apoptotic proteins: p53 [35, 36], Forkhead box class O (FOXO) transcription factors 1, 3a, and 4 [37–39], signal transducer and activator of transcription (STAT) 1 and 2 [40, 41], Hypoxia-inducible factors 1α (HIF-1α) [42, 43], breast cancer 1 (BRCA1) [44], SMA/MAD homology (Smad) proteins [45, 46], the Runt-related transcription factor (RUNX) [47], E2 Transcription Factor (E2F) [48], and E-proteins [49] (Table 1). The presence of multiple TADs in CBP/p300 and the wide array of interaction partners, many of which also have multiple TADs, allows for multivalent and combinatorial assembly of complexes [50, 51] (discussed below). CBP/p300 also acts as a coactivator for nuclear receptors. Rather

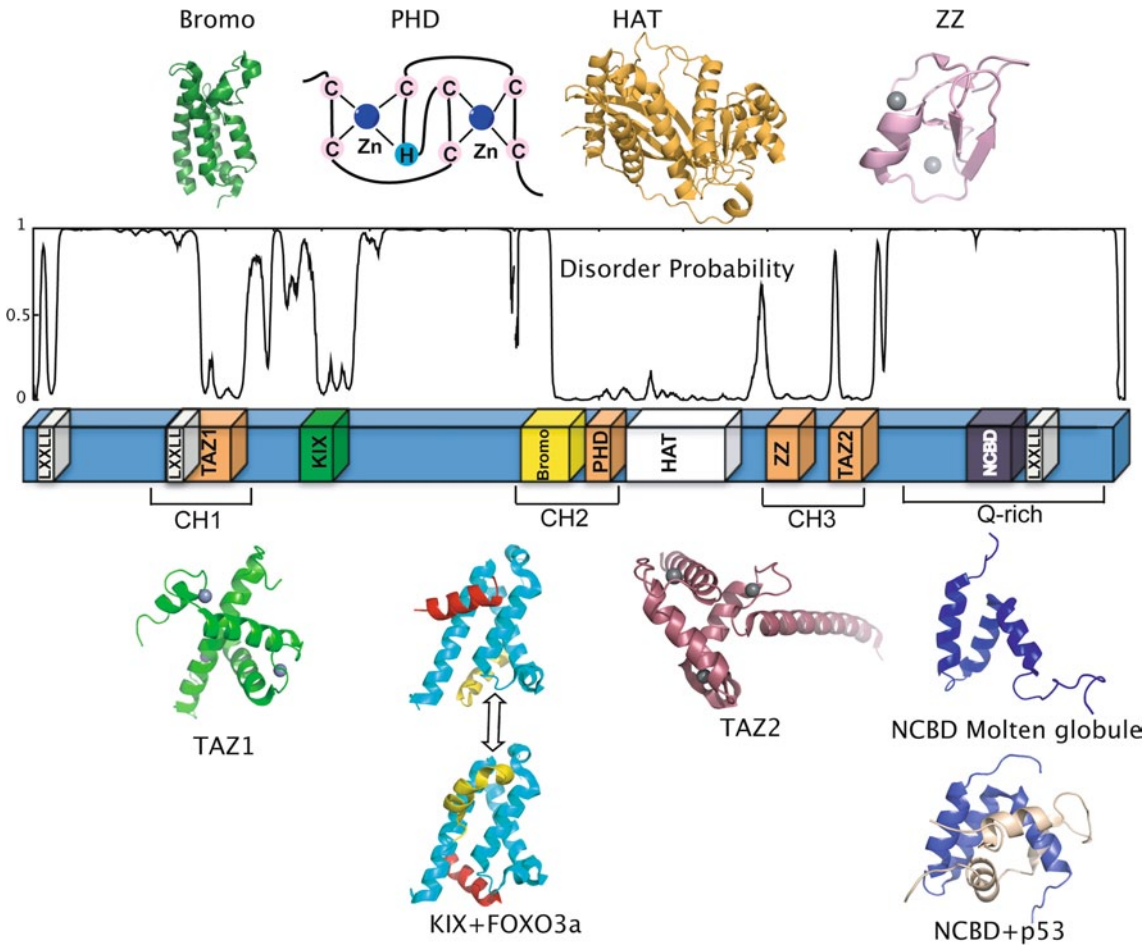


Fig. 2 Domain architecture and structures of domains of CBP/p300. The domain architecture of CBP/p300 is shown in the middle with the probability that regions are intrinsically disordered as predicted by DISOPRED2 [217]. The structures of each domain are also shown and labeled. *Top* the CBP Bromo domain (PDB: 3DWY); the Zn^{2+}-binding mode of the PHD domain of CBP/p300 (no high-resolution structure available); the p300 HAT domain in complex with an inhibitor (PDB: 3BIY); the CBP ZZ domain (PDB: 1TOT). *Bottom* the CBP TAZ1 domain (PDB: 1U2N); KIX domain in complex with FOXO3a CR2C-CR3 (note that KIX comprises two binding sites and the two FOXO3a TADs each bind both sites, thus CR2C-CR3 interacts with KIX in two distinct dynamically exchanging, equally populated orientations. PDB: 2LQH and 2LQI); the p300 TAZ2 domain (PDB: 3IO2); the molten globule state structure of CBP NCBD domain (PDB: 2KKJ), and the structured complex of NCBD with p53 formed through binding-coupled folding (PDB: 2L14). Transactivation domains that primarily interact with transcriptional activators are shown below and those that interact primarily with chromatin are shown on *top*

than the TADs, these interactions are mediated by short peptide motifs of CBP/p300, which are recognized by the activation function-2 (AF-2) region of the ligand-binding domains (LBDs) of nuclear receptors including retinoid X receptor (RXR) [52], androgen receptor (AR) [53], and estrogen receptor (ER) [54].

Through its cooperation with diverse transcription factors, CBP/p300 is involved in many cellular processes, and can promote diametrically opposed outcomes, i.e., apoptosis versus cell proliferation, dependent on the cell-type and context. In this review, we will focus on (1) the structural mechanisms of CBP/p300-transcription factor interactions, including the importance of intrinsically disordered regions (IDRs) and multivalent interactions, (2) the regulation of the coactivator function of CBP/p300 by post-translational modifications (PTMs), (3) roles for CBP/p300 in human diseases, especially cancer, and (4) the current efforts towards development of small molecules targeting CBP/p300 as potential therapeutics.

Interactions between CBP/p300 and basal transcription machinery and other coactivators

CBP/p300 associates with basal transcription machinery

CBP/p300 has been found to bind to some GTFs, such as TFIIB and TATA-box binding protein (TBP), and it

Table 1 Summary of CBP/p300 binding partners

Domain	Interaction partner	Category	Ref/PDB	Notes
TAZ1	TBP	General transcription factor	[59]	Mapped by GST-pull down
	p53	Transcription factor	[50, 100]	$K_d = 1$ μM, phosphorylation enhances binding
	FOXO3a	Transcription factor	[51]	$K_d = 71$ μM, S626 phosphorylation enhances binding
	HIF-1a	Transcription factor	[99, 104]/1L8C	$K_d = 7$ nM, Asparagine hydroxylation and S-nitrosylation of HIF-1α decreases binding
	CITED2	Transcription factor	[105–107]/1R8U, 1P4Q	$K_d = 13$ nM,
	STAT2	Transcription factor	[112]/2KA4	$K_d = 58$ nM
KIX (c-Myb site)	CREB (pKID)	Transcription factor	[19, 72–74]/1KDX	$K_d = 700$ nM for KID phophorylated at S133, which enhances binding. Phosphorylation on S111, 121, and 142 decreases binding
	c-Myb	Transcription factor	[77–79]/1SB0	$K_d = 15$ μM, cooperative with MLL in KIX binding
	p53	Transcription factor	[84]	AD1: $K_d = 242$ μM, AD2: $K_d = 94$ μM, AD1 and AD2 both bind the c-Myb site in each of two opposite orientations; phosphorylation enhances binding
	FOXO3a	Transcription factor	[51]/2LQH, 2LQI	CR2C-CR3 binding to the c-Myb site: $K_d = 258$ μM, S626 phosphorylation enhances the binding
KIX (MLL site)	MLL	Transcription factor	[79, 80]/2AGH	$K_d = 2.8$ μM, cooperative with c-Myb in KIX binding
	p53	Transcription factor	[84]	AD1: $K_d = 211$ μM, AD2: $K_d = 49$ μM; AD1 and AD2 both bind the MLL site in each of two opposite orientations; phosphorylation enhances binding
	FOXO3a	Transcription factor	[51]/2LQH, 2LQI	CR2C-CR3 binding to the MLL site: $K_d = 335$ μM, S626 phosphorylation enhances binding
	HTLV-1HBZ	Transcription factor	[85]	$K_d = 3$ nM, two helical TADs bind to one site cooperatively
	c-Jun	Transcription factor	[86]	$K_d = 30$ μM
	E2A	Transcription factor	[49, 88, 89]	$K_d = 12$ μM
	HTLV-1 Tax	Viral protein	[90]	Affinity is lower than that of MLL
KIX (two sites)	p53	Transcription factor	[84]	Full p53 TAD: AD1-AD2 binding to KIX: $K_d = 9.3$ μM; there are totally 8 distinct dynamically exchanging conformations
	FOXO3a	Transcription factor	[51]/2LQH, 2LQI	FOXO3a CR2C-CR3 binding to KIX: $K_d = 85$ μM; there are in two distinct dynamically exchanging, equally populated conformations
KIX (binding site unknown)	BRCA1	Transcription factor	[87]	Interaction requires methylation of CBP/p300 by CARM1
	SREBP	Transcription factor	[91]	
Bromo	Histone 4	Histone	[63]/2RNY	$K_d = 218$ μM, K20 acetylation is required
	p53	Transcription factor	[165]/1JSP	$K_d = 187$ μM, K382 acetylation is required
TAZ2	E1A	Adenoviral protein	[60, 108, 109]/2KJE	K_d is in low nM range
	TFIIB	General transcription factor	[60]	Displaced by E1A
	PCAF	Coactivator	[67]	Competes with E1A for CBP/p300 binding
	GCN5	Coactivator	[69]	Binding site is broader than PCAF
	p53	Transcription factor	[50, 100, 101]/2K8F	$K_d = 20$ nM, two p53-binding sites on TAZ2, phosphorylation enhances binding
	FOXO3a	Transcription factor	[51]	$K_d = 33$ μM, S626 phosphorylation enhances the binding
	STAT1	Transcription factor	[112]/2KA6	$K_d = 52$ nM
	MEF2	Transcription factor	[114–117]/3P57	K_d can not be determined due to multiple species in solution

Table 1 continued

Domain	Interaction partner	Category	Ref/PDB	Notes
NCBD (IBiD)	p53	Transcription factor	[50, 100, 112]/2L14	$K_d = 9.3$ μM; binding-coupled folding of NCBD; phosphorylation enhances binding
	IRF-3	Transcription factor	[118]/1ZOQ	Binding-coupled folding of NCBD
	ACTR	Coactivator	[27, 120, 121]/1KBH	$K_d = 34$ nM
LXXLL motifs	Retinoid X receptor	Nuclear receptor	[52]	Activation function-2 region of the ligand-binding domains of nuclear receptors interacts with one or more of the CBP/p300 LXXLL motifs
	Estrogen receptor	Nuclear receptor	[53]	
	Androgen receptor	Nuclear receptor	[54]	

can be co-purified with Pol II as a part of the RNA Pol II holoenzyme (Table 1). In HeLa cell nuclear extract, CBP is present in the RNA Pol II holoenzyme [55]; however, this association requires RNA helicase A, which suggests that the interaction is indirect [56]. These studies revealed one mechanism by which the binding of CBP to the transcriptional activator CREB promotes transactivation, confirming an adaptor role for the transcriptional coactivator CBP. Similarly, a direct interaction between RNA Pol II and p300 was observed, which may be enhanced by RNA helicase A [57]. Antibody-mediated depletion of CBP from the RNA Pol II holoenzyme reduced association of the basal transcription machinery components TFIIB and TBP [58], indicating that CBP provides the binding sites for TFIIB and TBP. Biochemical studies with recombinant proteins mapped the TBP-binding site to the N-terminal CH1/TAZ1 region [59], whereas TFIIB interacts with the TAZ2 zinc finger domain within the CH3 region [60]. Interestingly, both these GTF-binding sites overlap with those of the TADs of many transcriptional activators. CBP/p300 was demonstrated to acetylate TFIIEβ and TFIIF, suggesting that transient interactions occur between these proteins [61]. Although the interactions between CBP/p300 and these GTFs were characterized in vitro, the structural details are still elusive. More biochemical and structural investigation will be required to elucidate the mechanisms of basal transcription machinery recruitment by CBP/p300.

CBP/p300 cooperates with other transcriptional coactivators

CBP/p300 provides a docking platform not only for the components of the basal transcription machinery but also for some other transcriptional coactivators (Table 1), which cooperate in the efficient activation of gene transcription under various conditions. CBP/p300 interacts with the transcriptional coactivators p300/CBP association factor (PCAF) and GCN5, which comprise a related HAT family [62]. Relative to CBP/p300, these coactivators are structurally diverse and exhibit different substrate specificity in the histone targets of both their HAT activities and their acetyl-lysine-binding Bromo domains [63, 64]. Although PCAF and GCN5 can function independently [65, 66], in certain tissues, they interact with CBP/p300 and function synergistically. PCAF competes with E1A for CBP/p300 TAZ2 domain binding, and over-expression of PCAF in HeLa cells inhibits cell cycle progression [67]. Moreover, formation of a PCAF:CBP/p300 coactivator complex is required for CLOCK/BMAL1-mediated transcription in NIH3T3 cells [68]. Both N- and C-terminal regions of the coactivator GCN5 interact with CBP/p300 through a binding site that encompasses the TAZ2 domain as well as flanking regions, which is more extensive than the PCAF-binding site [69]. Cooperation between GCN5 and p300 increases the TGF-β-induced transcriptional activities of Smad transcription factors [70]. The reduced viability of mice lacking one allele of both GCN5 and p300 suggests that p300 cooperates specifically with GCN5 to provide essential functions during early embryogenesis [71].

Structural basis of CBP/p300-transcription factor interactions

CBP/p300 interacts with the sequence-specific DNA-binding transcription factors through its four conserved TADs. The well-characterized CBP/p300 TADs include the TAZ1 domain in the CH1 region, the KIX domain, the TAZ2 domain in the CH3 region, and the NCBD domain in the C-terminal Q-rich region (Fig. 2). These domains interact with the TADs of transcription factors, many of which are intrinsically disordered in isolation and undergo binding-coupled folding. The structures of CBP/p300 domains in complex with transcription factor TADs have been studied extensively (Table 1), and are discussed in the following sections. These studies have shed light on

the mechanisms of the coactivator recruitment step of transcription activation.

Transactivation domain interactions with the CREB-binding (KIX) domain

CBP was identified by its interaction with a phosphorylated form of the transcription factor CREB [19–21]. Protein kinase A (PKA) phosphorylates Ser133, which is located in the so-called kinase-inducible domain (KID) of CREB, and phosphorylated KID (pKID) specifically binds to the KIX domain of CBP/p300 [19, 72]. Several structures of KIX in complex with transcription factor TADs have been determined by solution nuclear magnetic resonance (NMR) spectroscopy, including the KIX–pKID complex [73]. The KIX domain is composed of a three-helix bundle with two additional short 3_{10} helices. The apo-pKID is largely unstructured, but residues 121–143 form two mutually perpendicular helices when bound to KIX [73]. The binding process is initiated by the formation of an encounter complex [74], and computational simulations showed that both conformational selection [75] and induced-fit [76] contribute to the interaction. pKID binds a hydrophobic groove formed by helices H1 and H3 of KIX, with a K_d of about 700 nM, which is ~100-fold tighter than unphosphorylated KID peptide. It was proposed that the mechanism by which phosphorylation enhances binding involves an interaction between the phosphate group and the side chain of KIX Y658 [24, 73, 77].

As structures of other TAD–KIX complexes were solved, a surprising degree of diversity in the binding modes of transactivation peptides was revealed. The TAD of the transcription factor c-Myb binds the same site as CREB (KIX H3–H4), but binds as a single helix [78]. Furthermore, a second site involved in the specific recognition of transactivation peptides was identified in the KIX domain. On the face of KIX opposite the H1–H3 groove, there is another hydrophobic groove, comprised of H2, H3, and the 3_{10} helix G2, which can be occupied by the TAD of the myeloid-lymphoid leukemia (MLL) protein. Remarkably, the c-Myb and MLL transcription factors bind to the two KIX sites simultaneously in a cooperative manner [77, 79, 80]. Comparing the ternary complex to the KIX-c-Myb structure, the association of MLL stabilizes the residues with which it interacts, and a subtle change propagated to the other binding site creates additional interactions with c-Myb [80].

Some transcription factors interact with the two KIX hydrophobic grooves in a promiscuous manner. CBP/p300 is the key coactivator of tumor suppressors FOXO3a and p53 [37, 38, 81, 82]. FOXO3a contains two TADs, called CR2C and CR3, which can each bind both KIX sites such that FOXO3a can associate with KIX in two different modes: CR2C bound to the c-Myb site and CR3 bound to the MLL site, or CR2C in the MLL site and CR3 in the c-Myb site (Fig. 2) [51, 83]. Both the c-Myb and MLL sites are very plastic, and the transactivation peptides from FOXO3a, CREB, c-Myb, and MLL bind to the KIX domain with different orientations, including opposite directions, apparently with minimal structural rearrangement of the KIX helices that form the binding site [51, 73, 80]. The structural plasticity of the KIX was further highlighted by the recent structure of KIX in complex with the first activation domain (AD1, also called p300/CBP and ETO target in E-proteins or PCET) of the E-protein E2A. The PCET peptide binds the MLL site in an orientation that differs from the MLL peptide, and the G2 helix of KIX is rearranged [49]. The interaction between p53 and CBP/p300 exhibits a remarkable degree of promiscuity, as each of the two subdomains of its TAD (AD1 and AD2) can bind both KIX sites in each of two opposite orientations, potentially enabling eight distinct association modes [84]. This complexity precluded determination of the structures. Another example that highlights the plasticity is the binding of the retroviral human T cell leukemia virus type 1 (HTLV-1) protein HBZ to KIX. HTLV-1 causes adult T cell leukemia by deregulating transcription. The HBZ protein binds to the MLL-site of KIX, both impairing MLL-mediated and enhancing c-Myb-mediated transcriptional activation through the allosteric connection between the two sites. HBZ contains two helical binding sites that were proposed to form a hairpin and interact simultaneously with the wide and shallow hydrophobic groove of the MLL-binding site [85].

In addition to the examples mentioned above, the KIX domain of CBP/p300 is able to accommodate peptides from a variety of other proteins, including c-Jun [86], BRCA 1 [87], E2A [88, 89], HTLV-1 Tax[90], and the sterol regulatory element binding protein (SREBP) [91] (Table 1). Sequence alignment of the KIX-interacting peptides from these proteins reveals a common "ϕXXϕϕ" motif, where ϕ is a hydrophobic residue, and X is an arbitrary residue. The "ϕXXϕϕ" sequence forms an amphipathic helix placing the hydrophobic residues in the binding site groove. Interestingly, despite the conservation of the "ϕXXϕϕ" motif, the exact mode of binding of "ϕXXϕϕ" peptides is clearly not conserved. The "ϕXXϕϕ" motif plays a number of important roles in many aspects of transcriptional regulation [92].

Transactivation domain interactions with the conserved zinc finger domains

There are four zinc finger motifs present in CBP/p300, including TAZ1, TAZ2, PHD, and ZZ. The structures of TAZ1, TAZ2, and ZZ have been determined [23, 93–95]. No structure of the CBP/p300 PHD domain is available; however, it is a C4HC3-type zinc finger motif [96], and structures of homologous domains from several other proteins have

been solved [97, 98]. Despite speculation that the PHD and ZZ domains may be involved in protein–protein interactions and ligand binding, the precise function of these domains remains elusive. In contrast, TAZ1 and TAZ2 have been well characterized as transactivation domains (Table 1). TAZ1 and TAZ2 are each comprised of four amphipathic helices that support three HCCC-type zinc-binding sites [23, 93, 99]. The structures of TAZ1 and TAZ2 are similar; however, the fourth helix is found in opposite orientations in the two domains (Fig. 2), a feature that was proposed to determine binding specificity for different activation domains [93].

The TADs of some activators are specific for TAZ1 or TAZ2, whereas some interact with both TAZ domains as well as other CBP/p300 TADs. For example, the highly promiscuous TAD of p53 binds to TAZ1 and TAZ2 [50, 100], as well as both sites of KIX and NCBD [50]. The solution structure of p53 AD1 in complex with TAZ2 shows that AD1 forms a helical structure and contacts TAZ2 through an extended hydrophobic surface with some electrostatic contributions [101]. Phosphorylation of S15 or T18 of p53 increases its affinity for TAZ2, through a combination of electrostatic interactions with nearby basic residues in TAZ2, and modulating the extent of hydrophobic interactions. A recent study suggests that both AD1 and AD2 of p53 bind TAZ2 at two coupled binding sites [102, 103]. A fusion peptide encompassing both TADs of FOXO3a (CR2C-CR3) also binds to both TAZ1 and TAZ2 in addition to KIX, but the detailed binding mode is unclear [51]. These results further reveal the complexity of the interaction between the IDRs of transcription factors and the TADs of CBP/p300.

In contrast to p53 and FOXO3a, the TADs of some transcription factors do exhibit specificity for TAZ1 or TAZ2. The TAZ1 domain recognizes the carboxyl-terminal activation domain (CAD) of HIF-1α, which functions in the maintenance of cellular oxygen homeostasis by inducing transcription of adaptive genes under hypoxic conditions [99, 104]. CAD, which is intrinsically disordered in isolation, encircles the TAZ1 domain with regions of extended conformation as well as three short binding-induced helices. A 'hypoxic switch' residue, N803, which is not hydroxylated under hypoxic conditions, is intimately involved in the interface. Under normal conditions, hydroxylation of this asparagine inhibits CBP/p300 binding and transactivation. The affinity of the HIF-1α CAD-TAZ1 interaction is very high, with a K_d of 7 nM [104]. CBP/p300-interacting transactivator 2 (CITED2) negatively regulates the activity of HIF-1α by competing for CBP/p300 binding [105–107]. CITED2 wraps around TAZ1 in a manner similar to HIF-1α, with a partially overlapping binding site, although it does not occupy the entire HIF-1α binding site. The K_d of CITED2 binding to TAZ1 is about 13 nM, comparable to that of HIF-1α [106].

The adenoviral protein E1A interacts with CBP/p300 primarily through TAZ2 to activate viral gene transcription [108], although interactions with the KIX and NCBD domains have also been reported [109, 110]. The unstructured CR1 region of E1A becomes partially helical upon binding the TAZ2 domain of CBP/p300 through extensive hydrophobic interactions [111]. The binding site of E1A overlaps that of the p53 TAD, and E1A can effectively displace p53. Recruitment of CBP/p300 by STAT proteins provides an excellent illustration of selectivity of the TAZ1 and TAZ2 domains. CBP TAZ1 and TAZ2 specifically recognize the TADs of STAT2 and STAT1, respectively, with over 100-fold selectivity. The TAD of STAT2 binds TAZ1 with an extended contact surface, similar to HIF-1α and CITED2, while STAT1 TAD interacts with TAZ2 through a hydrophobic surface [112]. Differences in helix packing between TAZ1 and TAZ2, and variations in the hydrophobic surfaces may determine this target selectivity.

Myocyte enhancer factor 2 (MEF2) is a transcription factor that controls muscle cell development, dopaminergic neuronal differentiation, and calcium-induced T cell apoptosis. MEF2 interacts with corepressors in the resting state, but, upon activation by Ca^{2+}, MEF2 dissociates from corepressors and engages coactivators including CBP/p300 [113]. The binding sites that mediate the MEF2–p300 interaction were mapped directly to the DNA-binding MADS-box/MEF2 domain of MEF2 and the TAZ2 domain of CBP/p300 [114–116]. Structural studies of this interaction employed an extended TAZ2 domain construct with an additional C-terminal helix (α4), relative to the construct used in previous NMR studies. Surprisingly, the crystal structure of a MEF2:TAZ2 complex in the presence of a double-stranded oligonucleotide containing a MEF2-binding element revealed three DNA-bound MEF2 dimers interacting simultaneously with three distinct surfaces of TAZ2 [117] (Table 1). The additional α4 helix comprises one of the MEF2-binding sites, whereas the other two binding sites partially overlap the p53- and STAT1-binding sites [117]. In contrast to the binding-coupled folding of intrinsically disordered TADs upon interaction with TAZ2, as discussed above, MEF2 binds largely by rigid-body docking of folded domains with no substantial change in the structure of TAZ2 or the MEF2 dimers. However, unlike the static picture presented by the crystal structure, these interactions are very dynamic, and, in solution, the complex exists in equilibrium between several species with different stoichiometries [117].

Transactivation domain interactions with the C-terminal NCBD domain

The NCBD domain within the C-terminal Q-rich region of CBP/p300 lacks well-defined structure in isolation; however,

upon interacting with the structured TAD of IRF-3, it adopts a well-defined structure [26, 118]. Interestingly, interactions between NCBD and the intrinsically disordered TADs of other transcription factors involve the synergistic folding and binding of two intrinsically disordered polypeptides. NCBD binds the TAD of p53, largely through hydrophobic interactions, and concomitantly NCBD adopts a three-helix bundle structure. AD1 and AD2 of p53 form helices that dock to adjacent patches on NCBD, whereas the loop connecting these helices is flexible and does not contact NCBD (Fig. 2) [119]. Similar results have also been reported for the complex of NCBD and activator of thyroid and retinoic acid receptors (ACTR), which is a transcription coactivator [27, 120, 121]. When in complex with ACTR, NCBD forms a structure similar to that seen in the NCBD–p53 complex, except that the length and orientation of the last helix differs [27]; however, these two structures differ substantially from the IRF-bound form of NCBD [118]. Biophysical characterization of ligand-free NCBD indicates a molten globule state with a small cooperatively folded core, which includes a transient conformer that resembles the ACTR and p53-bound states (Fig. 2) [122], thus the binding of ACTR and p53 to NCBD involve conformational selection [123].

Interactions between CBP/p300 LXXLL motifs and nuclear receptors

CBP/p300, as well as the p160 proteins NCoA-1, 2, and 3, are coactivators that mediate ligand-dependent gene expression through interactions with the ligand-binding domains (LBDs) of several nuclear receptors. Interaction of a ligand with its binding pocket in the LBD induces a structural rearrangement exposing a coactivator-binding site that recognizes LXXLL motifs in the coactivator [124, 125]. CBP/p300 contains three LXXLL motifs (Fig. 2), two of which mediate interactions with RXR [52], AR [53], and ER [54]. The polar residue preceding the LXXLL motif is important for the binding affinity and specificity [92].

Promiscuous multivalent interactions enable synergistic/antagonistic effects

IDRs are abundant in proteins involved in transcription, translation, and signal transduction (Fig. 3a). IDRs lack rigid three-dimensional structure, but are able to undergo binding-coupled folding and adopt multiple structures, which enable them to interact with a variety of binding partners [126, 127]. Many TADs of transcription factors are intrinsically disordered, and are capable of binding multiple sites on CBP/p300, as well as other transcription factors. As described above, p53 interacts with KIX, TAZ1, TAZ2, and NCBD [50, 128], while FOXO3a interacts with KIX, TAZ1, and TAZ2 [51]. Erythroid Kruppel-like factor (EKLF) also interacts with all four CBP/p300 activation domains [129], but these complexes await structural characterization. Furthermore, multiple binding interfaces have been identified with individual TADs of CBP/p300. For instance, FOXO3a occupies two sites within the KIX domain [51], and MEF2 dimer interacts with three distinct surfaces of the TAZ2 domain [117]. The promiscuous multivalent binding may contribute to the synergy of coactivator recruitment by groups of transcription factors that regulate similar biological processes. For example, FOXO3a and p53, which share similar functions and many common target genes, have been shown to interact with each other [130, 131], and proposed to assemble a transcriptional regulatory complex [132]. Thus, p53 and FOXO3a may simultaneously interact with multiple sites of CBP/p300, and synergistically stabilize the transcription factor–coactivator complex. Some transcription factors dimerize upon activation. For example, a STAT1/STAT2 heterodimer is able to associate with CBP/p300 through both the TAZ2 and TAZ1 sites, presumably enhancing the transcription efficiency [112, 133]. FOXO3a and Smad also form a heterodimer on the p21 gene promoter, and both are required for p21 gene transcription [134]. We speculate that the heterodimerization of activators enables multivalent binding, which improves the efficiency of CBP/p300 recruitment and therefore transcription of target genes. Recent studies found that more than half of human gene promoters contain conserved multiple binding sites for the same transcription factor in the ~100–1,000-base *cis*-regulatory modules, called homotypic clusters of transcription factor binding sites (HCTs). Transcription factors are enriched in these HCTs, and colocalization of the enhancer-associated CBP/p300 was observed at HCTs [135]. Thus, we propose a model that HCTs would promote the accumulation of transcription factors and the formation of multivalent interactions between the TADs of bound transcription factors and CBP/p300. The structure of three DNA-bound MEF2 dimers in complex with TAZ2 [117] provides insight into the assembly of such a multivalent complex, which could be extended by involvement of other CBP/p300 TADs. Moreover, the tandem TADs located in extended IDRs of many transcription factors, including p53, FOXO3a, and c-Myc, would further contribute to the multivalent association (Fig. 3). Individual TADs interact weakly with CBP/p300; however, the product of multiple weak binding events would stabilize the interaction, promoting coactivator recruitment and initiation of gene transcription. IDRs in both CBP/p300 and transcriptional activators may adopt different conformations to accommodate local chromatin structure and the variable distance to the transcription start site, allowing CBP/p300 to be positioned correctly to promote transcription initiation. Furthermore, multivalent binding may provide a mechanism by which some transcription factors modulate the effect of

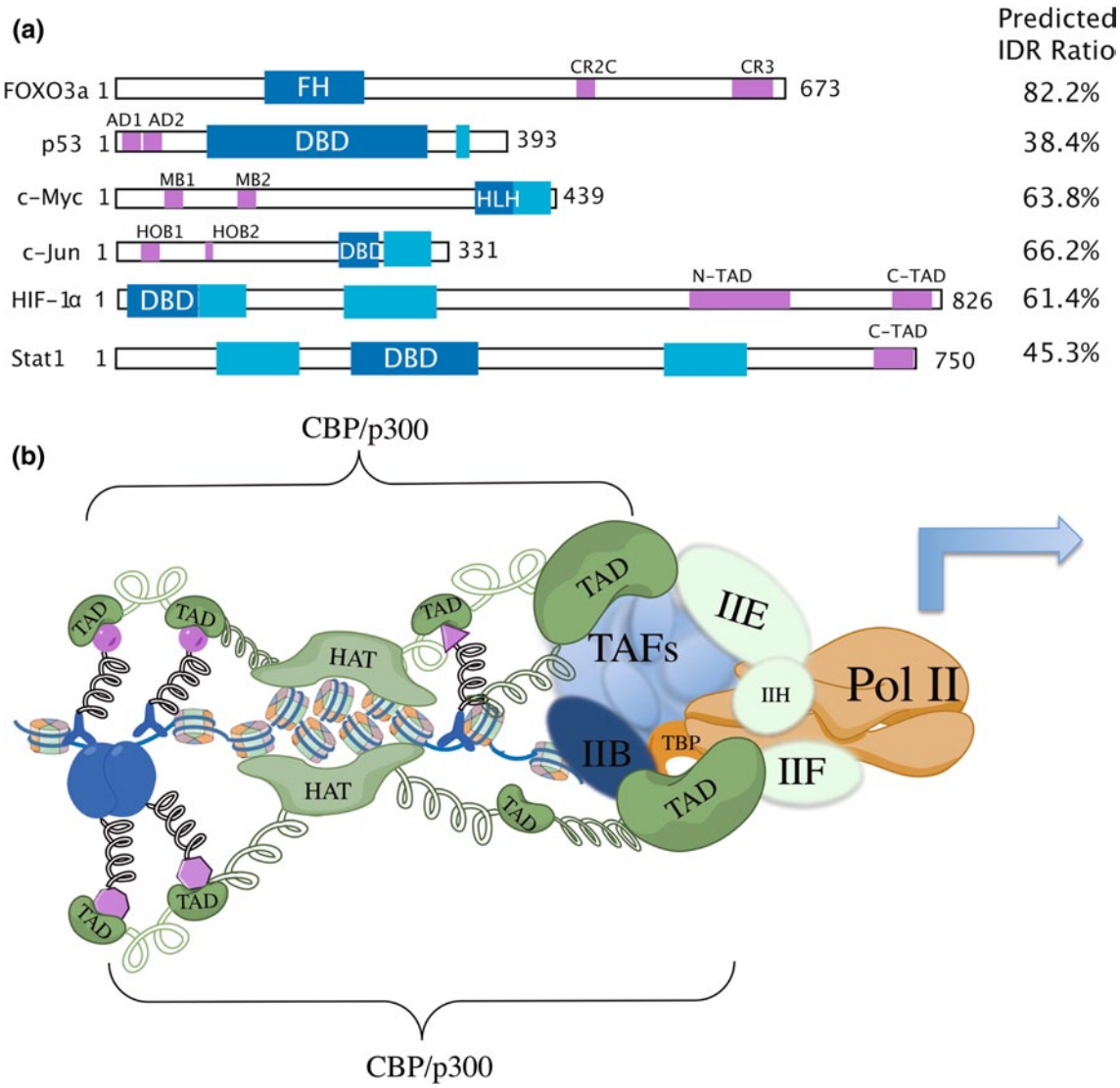


Fig. 3 Promiscuous multivalent model of CBP/p300 recruitment. **a** Many transcription factors contain tandem TADs located in intrinsically disordered regions (IDRs). DNA-binding domains are shown as *blue boxes*, other structured domains are indicated as *cyan boxes*, and TADs are labeled and colored *purple*. Uncoloured regions and most TADs are predicted IDRs, and the percentage of each transcription factor that is comprised of IDRs is indicated. **b** Multivalent binding model of CBP/p300 recruitment by transcription factors. In the promoter and enhancer regions, there are multiple transcription factor binding sites (TFBSs) for one or more transcription factors. Each TAD interacts weakly with CBP/p300; however, the product of multiple weak binding events would stabilize the interaction, promoting recruitment and initiation of gene transcription. Some transcription factors function as homo- or hetero-dimers, of which each monomer unit may interact with different TADs of CBP/p300 (*bottom*), recruiting coactivator CBP/p300 more efficiently through multivalent interactions and avoiding competition for one binding site. The IDRs present in CBP/p300 as well as the transcription factors may facilitate recruitment of CBP/p300 in a productive orientation and position, adapting to various chromatin structures

other transcription factors. For example, FOXO3a is able to inhibit HIF-1α transactivation through forming a ternary complex with CBP/p300 and HIF-1α, as well as by activating transcription of its inhibitor CITED2 [136, 137]. The mechanism is unknown, but formation of a ternary complex is essential. In addition to TAZ1, which binds HIF-1α very tightly, FOXO3a also binds to the KIX and TAZ2 domains, which may enable the formation of the ternary complex.

Regulation of CBP/p300-transcription factor interaction by PTMs

Transcription factors recruit the coactivator CBP/p300 to activate transcription of their target genes. The intrinsically disordered TADs of transcription factors are readily accessible to PTM enzymes, and, in response to various stimuli, the interactions between CBP/p300 and transcription factors

are extensively regulated by modifications of both classes of proteins [138]. These PTMs both positively and negatively regulate the association of transcription factors with CBP/p300 (Table 1). Phosphorylation on S133 of the KID domain of CREB increases the binding affinity to CBP/p300 [73], whereas phosphorylation of S142 by calcium- and calmodulin-dependent kinase II (CaMKII) [139], and S111 and S121 by ataxia-telangiectasia mutated (ATM) [140, 141] inhibit CREB binding [142]. The TAD of p53 also contains several phosphorylatable Ser residues, and their phosphorylation increases the binding of p53 to all four TADs of CBP/p300 in a graded manner [128, 143, 144]. Likewise, AMPK phosphorylation of S626 of FOXO3a also enhances the binding affinity of FOXO3a CR3 to the KIX and TAZ1/2 domains [51]. Asparagine hydroxylation and S-nitrosylation of HIF-1α CAD decreases CBP/p300 binding, whereas phosphorylation does not affect CBP/p300 binding, but may modulate HIF-1α transcriptional activity through interactions with other proteins [145].

Phosphorylation of CBP/p300 itself is another mechanism that modulates association with transcription factors. Phosphorylation of S436 of CBP (not conserved in p300) inhibits CREB–CBP interaction in hepatic cells [146, 147], even though this site is close to the C-terminus of TAZ1 and >100 residues away from the KIX domain. The mechanism by which S436 phosphorylation impairs CREB binding to KIX is unknown, but it is transcription factor-specific, as it does not affect FOXO binding [147]. Conversely, S436 phosphorylation is required for CBP/p300 binding to Pit-1 and AP-1 transcription factors, where it may enhance their interactions with the TAZ1 domain [148]. CBP/p300 is also modified by methylation. The coactivator-associated arginine methyltransferase 1 (CARM1) methylates R754 in the KIX domain of p300, creating a site that is recognized by BRCT domains of BRCA1, and this interaction is essential for the expression of the critical cell cycle and proliferation inhibitor p21 [87]. Overall, these PTMs of both CBP/p300 and transcription factors function to fine tune gene transcription.

The intrinsic acetyltransferase activity of CBP/p300

Histone modification and chromatin remodeling

The N-terminal tails of histone proteins are subject to many PTMs, including phosphorylation [149], methylation [150], ubiquitination [151], sumoylation [152], and acetylation [153]. Combinations of these modifications, defined as the "histone code", contribute to the alteration of chromatin structure, which regulates the expression level of genes [154]. Factors that covalently modify histones are defined as histone code "writers" [155]. CBP/p300 contains a HAT domain that acetylates nucleosomal histones in the proximity of the promoter to which CBP/p300 is recruited [13, 14]. Whether the acetyltransferase activity of CBP/p300 or its adapter function plays the major role in gene transcription is promoter–activator-specific. Histone acetylation relaxes the chromatin structure and makes chromosomal DNA more accessible [156]. It was shown in vitro that p300 acetylates all acetylation sites of histones H2A and H2B, and preferentially acetylates K14 and K18 of H3 and K5 and K8 of H4 [157]. Recent studies showed that CBP/p300 also acetylates K56 of H3, which has a critical role in DNA packing rather than chromatin relaxation [158], and deletion of CBP/p300 specifically and dramatically reduces acetylation on H3 K18 and K27 [64]. The structure of the HAT domain of p300 suggests that it applies a 'hit-and-run' (Theorell–Chance) catalytic mechanism in histone acetylation, in which, after binding of acetyl-CoA, the lysyl residue of the substrate peptide snakes through the p300 tunnel and reacts with the acetyl group. This mechanism is distinct from other characterized HATs, which explains the specificity and selectivity of the HAT activity of CBP/p300 (Fig. 2) [159, 160].

The viral protein E1A and the endogenous protein E1A-like inhibitor of differentiation 1 (EID-1) alter gene expression in part by inhibiting p300-dependent transcription. E1A is a multifunctional protein with an N-terminal CR1 region that interacts with TAZ2 as described above, as well as a C-terminal region that directly interacts with the HAT domain and inhibits HAT activity of both CBP/p300 and PCAF [161]. CR1 is not required for HAT inhibition, but likely facilitates the interaction by tethering E1A to CBP/p300. EID-1 is enriched in muscle tissue and can inhibit the expression of muscle-specific genes through tissue-specific transcription factors including MyoD and MEF2. EID-1 binding to CBP/p300 was mapped to the CH3 region (which includes TAZ2); however, it has been demonstrated that, like E1A, EID-1 regulates transcriptional activity largely by inhibiting CBP/p300 HAT activity [162, 163]. Suppression of CBP/p300 by EID-1 is associated with inhibition of myogenesis as well as pathogenesis of Alzheimer's disease [162, 164], and thus this protein–protein interaction may be an attractive target for certain pathological conditions.

The Bromo and PHD domains adjacent to the HAT domain are dispensable for histone acetylation, but were found to bind acetylated nucleosomes and transcription factors [28, 63, 165], and are thus considered histone code "readers" that play roles in epigenetic regulation (Fig. 2).

Acetylation of non-histone transcription factors by CBP/p300

The HAT activity of CBP/p300 also acetylates non-histone substrates, including transcription factors, which can positively or negatively modulate their activity through diverse

mechanisms. The C-terminal tail of p53 possesses non-specific DNA-binding activity, which interferes with its sequence-specific DNA-binding. Acetylation of the C-terminus by CBP/p300 reduces the non-specific DNA-binding of p53, and in turn increases its sequence-specific DNA-binding activity, thus forming a positive-feedback loop [166]. Similarly, acetylation of the MEF2 TAD by CBP/p300 enhances its DNA-binding and transactivation activity [167]. Smad-dependent transcription is also promoted by p300-mediated acetylation of Smad proteins; however, the mechanism involves facilitating their nuclear accumulation [168]. Transactivation activity of CREB is enhanced by CBP-mediated acetylation of sites within the CREB TAD, which presumably increases its binding to the KIX domain [169]. CBP/p300 acetylates the transactivation domain AD1 of E2A protein, and similar to CREB, this enhances the interaction between AD1 and KIX [170]. On the other hand, CBP/p300 acetylates the DNA-binding FH domain of FOXO3a and FOXO1, which impairs DNA-binding, thus forming a negative-feedback loop [171, 172]. CBP/p300 acetylation inhibits transactivation by the transcription factor TCF by disrupting its interaction with other co-factors [173].

The role of CBP/p300 in cancer and other human diseases

CBP/p300 interacts with a large number of transcription factors and is involved in a wide array of cellular activities, such as DNA repair, cell growth, differentiation, and apoptosis [16]. Thus, mutations of the CBP and p300 genes and dys-regulation of the proteins have been implicated in many human diseases, including cancer. Germline mutations (point mutations, translocations or deletions) of the CBP gene (but rarely p300) result in Rubinstein–Taybi syndrome, which is characterized by broad thumbs and cranio-facial and cardiac abnormalities, as well as mental retardation. Importantly, the patients also have increased predisposition to childhood malignancies [174–176]. $CBP^{+/-}$ mice have increased incidence of hematologic malignancies, which support a tumor suppressor function for CBP [177]. Actually, CBP/p300 is essential for hematopoietic homeostasis. The chimeric, oncogenic E2A-PBX1a and E2A-PBX1b proteins, present in ~5 % of acute lymphoblastic leukemia (ALL), interact with the KIX domain of CBP/p300, and this interaction is associated with accelerated cell proliferation [88]. In vivo studies of p300 showed that deletion of the KIX or CH1 domain causes profound and pervasive defects in hematopoiesis, whereas loss of most other domains has a minor effect [178]. Mutations in some transcription factors that interact with CBP/p300 are also associated with tumorigenesis. For example, recent high-throughput sequencing studies of non-Hodgkin lymphomas identified several mutations predicted to impair the activity of the HAT domains of CBP and p300, and further revealed that MEF2B is among the most frequently mutated genes in non-Hodgkin lymphomas [179]. Recurrent mutations in MEF2 were identified at the CBP/p300-binding interface and the DNA-binding site, presumably impairing recruitment of CBP/p300 to MEF2 target genes [179].

Chromosomal translocations directly involving the CBP or p300 genes are also associated with leukemia/lymphoma. Monocytic leukemia zinc-finger protein (MOZ) becomes fused to the amino-terminus of CBP or, more rarely, to p300 [in the t(8, 16) or t(8, 22) translocations, respectively] [180, 181], which are associated with acute myeloid leukemia (AML). MLL also forms fusion proteins with CBP [t(11, 16)] and p300 [t(11,22)] through chromosomal translocation [182–185], and these fusion proteins contribute to AML through gain-of-function. Both the Bromo and HAT domains are present in the chimeric proteins, and are necessary for immortalizing myeloid progenitors [186].

The findings discussed above suggest CBP and p300 can act as tumor suppressors, and indeed genetic alteration of these two genes results in carcinogenesis. CBP/p300 is important for the transactivation function of p53, BRCA1, and FOXO3a, which are all critical tumor suppressors; however, as a coactivator of c-Myc, c-Myb, and AR, CBP/p300 can also promote cell proliferation and cancer development under specific conditions. In fact, by activating AR-dependent transcription, CBP/p300 promotes prostate cancer progression, which can be blocked by siRNA against p300 [187, 188]. CBP/p300 also promotes cancer progression in colon cancer cell lines with microsatellite instability [189]. In some cancer treatments, CBP/p300 plays a role in the development of drug resistance: p300 mediates resistance to doxorubicin in bladder cancer [190], and the interaction between CBP and β-catenin is associated with breast cancer and acute lymphoblastic leukemia (ALL) drug resistance [191–193]. In addition to cancer, the interplay of CBP/p300 with different transcription factors is involved in HIV (activation of HIV gene expression through interaction with HIV-1 Tat) [194], Alzheimer's disease (interaction between CREB and CBP/p300 is disrupted by amyloid-β) [195], diabetes [impairment of interactions between pancreas duodenum homeobox (PDX-1) and p300] [196], and heart disease (essential role in embryonic heart development, but high expression levels of p300 drive myocardial hypertrophy through MEF2) [197, 198].

CBP/p300 as a drug target

Given the importance of deregulation of CBP/p300 in cancer and other human diseases, and its role in cooperating

with oncogenic transcription factors, efforts have been made in targeting CBP/p300 with small molecule inhibitors [199]. The availability of an extensive body of structural information on the TADs, Bromo domain, and HAT domain, as well as complexes formed by CBP/p300 and its binding partners, provides a good basis for inhibitor design. Some compounds have been designed to modulate the histone modification function of CBP/p300 (Fig. 4). Curcumin (diferuloylmethane), a natural product from the spice tumeric, is a specific inhibitor of CBP/p300 HAT activity, and represses the CBP/p300 HAT-dependent transcriptional activation from chromatin [200]. Curcumin represses acetylation of the HIV-Tat protein and HIV replication, but it also represses p53 acetylation, potentially inactivating this key tumor suppressor [200], and appears to have multiple, unrelated protein targets [201]. LTK-14 is a p300-selective

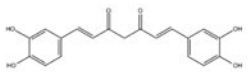
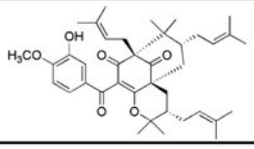
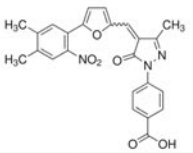
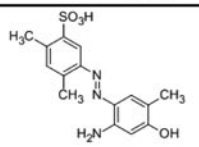
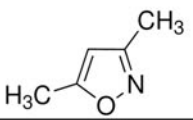
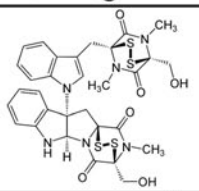
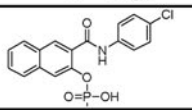
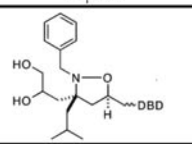
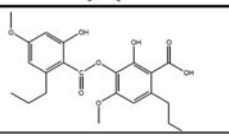
Name	Structure	Targeted domain	IC_{50}/K_d(μM)	Ref
Curcumin		HAT	IC_{50}=25	[200,201]
LTK-14		HAT	IC_{50}=5-7	[202,203]
C646		HAT	IC_{50}=1.6	[204]
Ischemin		Bromo	IC_{50}=5	[208]
3,5-dimethyl-isoxazole		Bromo	IC_{50}=28	[209]
Chetomin		TAZ1	IC_{50}=1.5	[211]
KG-501		KIX	IC_{50}=2.9	[212, 213]
iTAD		KIX	K_d=38	[214]
Depside sekikaic acid		KIX	IC_{50}=34 (MLL) IC_{50}=64 (KID)	[215]

Fig. 4 Compounds that target CBP/p300. Common names of compounds are indicated along with their chemical structures, the CBP/p300 domain targeted, and reported K_d or IC_{50} values

noncompetitive inhibitor for both acetyl-CoA and histone that inhibits the HAT activity of p300 but not PCAF and shows similar effects as curcumin [202, 203]. The recently developed compound C646 targets the CBP/p300 HAT domain, and induces apoptosis in prostate cancer cells, suggesting that CBP/p300 HAT inhibitors could serve as new anti-tumor therapeutics [204].

Bromo domains, which recognize acetylated peptide substrates, are found in several proteins and are emerging drug targets for many diseases (Fig. 4) [205, 206]. The CBP/p300 Bromo domain is important for p300 to maintain histone acetylation and effective gene transcription, and plays a key role in the cell transformation by the MLL-CBP/p300 fusion protein in AML [186, 207]. Ischemin, a small molecule that binds the Bromo domain of CBP, prevents apoptosis in cardiomyocytes with wild-type p53, and thus may protect normal tissues from apoptosis when used in combination with chemo- and radiation-therapies [208]. The importance of the Bromo domain to the transforming activity of MLL-CBP/p300 suggests that ischemin may be beneficial for acute leukemia treatment; however, this has not been examined. The 3, 5-dimethylisoxazole derivatives have been reported to bind to the CBP/p300 Bromo domain, but they also bind to the BET Bromo domain-containing proteins [209]. Thus, the selectivity of the inhibitor is crucial for targeting the CBP/p300 Bromo domain.

CBP/p300 is an important coactivator for many oncogenes, but its role as a coactivator for some tumor suppressors should be considered in any strategy to inhibit this important protein. Because tumor suppressor genes have been mutated or inactivated in many cancer cells, blocking the interactions between CBP/p300 and oncogenic transcription factors has been considered as a potential strategy for tumor treatment, and thus efforts have been made towards discovery of small molecule inhibitors of the CBP/p300 TADs (Fig. 4). The natural product chetomin was identified in a high-throughput screen as a molecule that disrupts the interaction between HIF-1α and the TAZ1 domain of CBP/p300, thus inhibiting hypoxia-inducible transcription and reducing tumor growth in vitro [210]. Chetomin inspired the design of synthetic dimeric epidithiodiketopiperazine molecules, which showed better disruption of HIF-1α binding with an IC_{50} of 1.5 ± 0.2 μM and lower toxicity than chetomin [211]. The KIX domain has also been an attractive target for inhibitor discovery. Using NMR spectroscopy, a small molecule (Naphthol AS-E phosphate or KG-501) was identified that interacts with both TAD-binding sites of KIX (i.e., the c-Myb and MLL sites), and inhibits CREB-binding [212]. Further characterization revealed that the compound is activated by dephosphorylation, and that Naphthol AS-E is a more effective KIX inhibitor [213]. Amphipathic small molecules that mimic the transcription factor TADs (iTAD) have been developed and shown to specifically bind the MLL-site of KIX and disrupt MLL-binding [214]. Screening of a library of natural products isolated from marine organisms identified several compounds capable of releasing the MLL TAD from a pre-assembled complex with the KIX domain. The lichen-derived depside sekikaic acid competes with MLL for binding to its site (IC_{50} of 34 μM), but further inhibits binding of KID at the c-Myb site (IC_{50} of 64 μM), possibly through the allosteric communication between the two sites, and was shown to down-regulate c-Jun-mediated gene expression in a cell-based assay [215]. These KIX inhibitors await testing in animal models. In addition to those discussed above, there are other compounds identified through functional screening, including ICG-001 [191] and Arylsulfonamide KCN1 [216] that are able to interfere with interactions between CBP/p300 and transcription factors, but how these molecules interact with CBP/p300 is unknown.

Summary and conclusions

In the past 15 years, exciting findings have been made through structural and functional studies of the transcriptional coactivator CBP/p300, which together demonstrate that CBP/p300 is very versatile and functions in many physiological and pathological processes. CBP/p300 interacts with transcription factors, many of which possess IDRs and engage in promiscuous multivalent binding with CBP/p300 (Table 1). This is essential in stabilizing a promoter-anchored transcriptional complex and promoting productive coactivator recruitment (Fig. 1). In the HCTs, IDRs are of particular importance as they can facilitate productive positioning of CBP/p300 with respect to a variable chromatin structure depending on epigenetic marks and gene-specific promoter structures. Another layer of transcriptional regulation involves post-translational modification of CBP/p300. Moreover, CBP/p300 itself can modify other transcription factors such as p53 acetylation, together generating a wide spectrum of transcriptional/epigenetic regulatory mechanisms. These are in parallel with cellular observations in which CBP/p300 was found to behave differently according to developmental stages and cell types. Much deeper understanding of both molecular and cellular mechanisms and actions of CBP/p300-dependent transcriptional regulation requires (1) systematic ways to visualize the spatiotemporal expression pattern of CBP/p300 in different tissues and cell types, and (2) global approaches to characterize the ratio of CBP/p300 that associates with different transcription factors in all normal and cancer cells. These cellular and proteomic approaches, combined with efforts in CBP/p300-targeted inhibitor screening, may yield a successful outcome for anti-cancer drug development. Currently available CBP/p300 inhibitors suffer from lack of specificity, and hence the advancement of structural understanding

of CBP/p300 interactions with various targets, combined with chemical and systems biology approaches, is absolutely needed for the development of better therapeutics in the personalized medicine era.

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References

1. Guarente L (1995) Transcriptional coactivators in yeast and beyond. Trends Biochem Sci 20(12):517–521. doi:S0968-0004(00)89120-3
2. Thomas MC, Chiang CM (2006) The general transcription machinery and general cofactors. Crit Rev Biochem Mol Biol 41(3):105–178. doi:10.1080/10409230600648736
3. Ptashne M, Gann A (1997) Transcriptional activation by recruitment. Nature 386(6625):569–577. doi:10.1038/386569a0
4. Workman JL, Roeder RG (1987) Binding of transcription factor TFIID to the major late promoter during in vitro nucleosome assembly potentiates subsequent initiation by RNA polymerase II. Cell 51(4):613–622. doi:0092-8674(87)90130-9
5. Horikoshi M, Hai T, Lin YS, Green MR, Roeder RG (1988) Transcription factor ATF interacts with the TATA factor to facilitate establishment of a preinitiation complex. Cell 54(7):1033–1042. doi:0092-8674(88)90118-3
6. Zhou J, Zwicker J, Szymanski P, Levine M, Tjian R (1998) TAFII mutations disrupt Dorsal activation in the Drosophila embryo. Proc Natl Acad Sci USA 95(23):13483–13488
7. Meisterernst M, Roeder RG (1991) Family of proteins that interact with TFIID and regulate promoter activity. Cell 67(3):557–567. doi:0092-8674(91)90530-C
8. Dynlacht BD, Hoey T, Tjian R (1991) Isolation of coactivators associated with the TATA-binding protein that mediate transcriptional activation. Cell 66(3):563–576. doi:0092-8674(81)90019-2
9. Kim YJ, Bjorklund S, Li Y, Sayre MH, Kornberg RD (1994) A multiprotein mediator of transcriptional activation and its interaction with the C-terminal repeat domain of RNA polymerase II. Cell 77(4):599–608. doi:0092-8674(94)90221-6
10. Bednar J, Horowitz RA, Grigoryev SA, Carruthers LM, Hansen JC, Koster AJ, Woodcock CL (1998) Nucleosomes, linker DNA, and linker histone form a unique structural motif that directs the higher-order folding and compaction of chromatin. Proc Natl Acad Sci USA 95(24):14173–14178
11. Naar AM, Lemon BD, Tjian R (2001) Transcriptional coactivator complexes. Annu Rev Biochem 70:475–501. doi:10.1146/annurev.biochem.70.1.475
12. Spiegelman BM, Heinrich R (2004) Biological control through regulated transcriptional coactivators. Cell 119(2):157–167. doi:10.1016/j.cell.2004.09.037
13. Bannister AJ, Kouzarides T (1996) The CBP co-activator is a histone acetyltransferase. Nature 384(6610):641–643. doi:10.1038/384641a0
14. Ogryzko VV, Schiltz RL, Russanova V, Howard BH, Nakatani Y (1996) The transcriptional coactivators p300 and CBP are histone acetyltransferases. Cell 87(5):953–959. doi:S0092-8674(00)82001-2
15. Shiama N (1997) The p300/CBP family: integrating signals with transcription factors and chromatin. Trends Cell Biol 7(6):230–236. doi:10.1016/S0962-8924(97)01048-9
16. Kalkhoven E (2004) CBP and p300: HATs for different occasions. Biochem Pharmacol 68(6):1145–1155. doi:10.1016/j.bcp.2004.03.045
17. Whyte P, Williamson NM, Harlow E (1989) Cellular targets for transformation by the adenovirus E1A proteins. Cell 56(1):67–75. doi:0092-8674(89)90984-7
18. Eckner R, Ewen ME, Newsome D, Gerdes M, DeCaprio JA, Lawrence JB, Livingston DM (1994) Molecular cloning and functional analysis of the adenovirus E1A-associated 300-kD protein (p300) reveals a protein with properties of a transcriptional adaptor. Genes Dev 8(8):869–884
19. Chrivia JC, Kwok RP, Lamb N, Hagiwara M, Montminy MR, Goodman RH (1993) Phosphorylated CREB binds specifically to the nuclear protein CBP. Nature 365(6449):855–859. doi:10.1038/365855a0
20. Kwok RP, Lundblad JR, Chrivia JC, Richards JP, Bachinger HP, Brennan RG, Roberts SG, Green MR, Goodman RH (1994) Nuclear protein CBP is a coactivator for the transcription factor CREB. Nature 370(6486):223–226. doi:10.1038/370223a0
21. Arias J, Alberts AS, Brindle P, Claret FX, Smeal T, Karin M, Feramisco J, Montminy M (1994) Activation of cAMP and mitogen responsive genes relies on a common nuclear factor. Nature 370(6486):226–229. doi:10.1038/370226a0
22. Bhattacharya S, Michels CL, Leung MK, Arany ZP, Kung AL, Livingston DM (1999) Functional role of p35srj, a novel p300/CBP binding protein, during transactivation by HIF-1. Genes Dev 13(1):64–75
23. De Guzman RN, Liu HY, Martinez-Yamout M, Dyson HJ, Wright PE (2000) Solution structure of the TAZ2 (CH3) domain of the transcriptional adaptor protein CBP. J Mol Biol 303(2):243–253. doi:10.1006/jmbi.2000.4141
24. Parker D, Ferreri K, Nakajima T, LaMorte VJ, Evans R, Koerber SC, Hoeger C, Montminy MR (1996) Phosphorylation of CREB at Ser-133 induces complex formation with CREB-binding protein via a direct mechanism. Mol Cell Biol 16(2):694–703
25. Albanese C, D'Amico M, Reutens AT, Fu M, Watanabe G, Lee RJ, Kitsis RN, Henglein B, Avantaggiati M, Somasundaram K, Thimmapaya B, Pestell RG (1999) Activation of the cyclin D1 gene by the E1A-associated protein p300 through AP-1 inhibits cellular apoptosis. J Biol Chem 274(48):34186–34195
26. Lin CH, Hare BJ, Wagner G, Harrison SC, Maniatis T, Fraenkel E (2001) A small domain of CBP/p300 binds diverse proteins: solution structure and functional studies. Mol Cell 8(3):581–590. doi:S1097-2765(01)00333-1
27. Demarest SJ, Martinez-Yamout M, Chung J, Chen H, Xu W, Dyson HJ, Evans RM, Wright PE (2002) Mutual synergistic folding in recruitment of CBP/p300 by p160 nuclear receptor coactivators. Nature 415(6871):549–553. doi:10.1038/415549a
28. Ragvin A, Valvatne H, Erdal S, Arskog V, Tufteland KR, Breen K, AM OY, Eberharter A, Gibson TJ, Becker PB, Aasland R (2004) Nucleosome binding by the bromodomain and PHD finger of the transcriptional cofactor p300. J Mol Biol 337(4):773–788. doi:10.1016/j.jmb.2004.01.051
29. Iyer NG, Ozdag H, Caldas C (2004) p300/CBP and cancer. Oncogene 23(24):4225–4231. doi:10.1038/sj.onc.1207118
30. Vervoorts J, Luscher-Firzlaff JM, Rottmann S, Lilischkis R, Walsemann G, Dohmann K, Austen M, Luscher B (2003) Stimulation of c-MYC transcriptional activity and acetylation by recruitment of the cofactor CBP. EMBO Rep 4(5):484–490. doi:10.1038/sj.embor.embor821
31. Dai P, Akimaru H, Tanaka Y, Hou DX, Yasukawa T, Kanei-Ishii C, Takahashi T, Ishii S (1996) CBP as a transcriptional coactivator of c-Myb. Genes Dev 10(5):528–540
32. Bannister AJ, Oehler T, Wilhelm D, Angel P, Kouzarides T (1995) Stimulation of c-Jun activity by CBP: c-Jun residues

Ser63/73 are required for CBP induced stimulation in vivo and CBP binding in vitro. Oncogene 11(12):2509–2514
33. Bannister AJ, Kouzarides T (1995) CBP-induced stimulation of c-Fos activity is abrogated by E1A. EMBO J 14(19):4758–4762
34. Patel D, Huang SM, Baglia LA, McCance DJ (1999) The E6 protein of human papillomavirus type 16 binds to and inhibits co-activation by CBP and p300. EMBO J 18(18):5061–5072. doi:10.1093/emboj/18.18.5061
35. Avantaggiati ML, Ogryzko V, Gardner K, Giordano A, Levine AS, Kelly K (1997) Recruitment of p300/CBP in p53-dependent signal pathways. Cell 89(7):1175–1184. doi:S0092-8674(00)80304-9
36. Lill NL, Grossman SR, Ginsberg D, DeCaprio J, Livingston DM (1997) Binding and modulation of p53 by p300/CBP coactivators. Nature 387(6635):823–827. doi:10.1038/42981
37. Nasrin N, Ogg S, Cahill CM, Biggs W, Nui S, Dore J, Calvo D, Shi Y, Ruvkun G, Alexander-Bridges MC (2000) DAF-16 recruits the CREB-binding protein coactivator complex to the insulin-like growth factor binding protein 1 promoter in HepG2 cells. Proc Natl Acad Sci USA 97(19):10412–10417. doi:10.1073/pnas.190326997
38. So CW, Cleary ML (2002) MLL-AFX requires the transcriptional effector domains of AFX to transform myeloid progenitors and transdominantly interfere with forkhead protein function. Mol Cell Biol 22(18):6542–6552
39. So CW, Cleary ML (2003) Common mechanism for oncogenic activation of MLL by forkhead family proteins. Blood 101(2):633–639. doi:10.1182/blood-2002-06-1785
40. Zhang JJ, Vinkemeier U, Gu W, Chakravarti D, Horvath CM, Darnell JE Jr (1996) Two contact regions between Stat1 and CBP/p300 in interferon gamma signaling. Proc Natl Acad Sci USA 93(26):15092–15096
41. Bhattacharya S, Eckner R, Grossman S, Oldread E, Arany Z, D'Andrea A, Livingston DM (1996) Cooperation of Stat2 and p300/CBP in signalling induced by interferon-alpha. Nature 383(6598):344–347. doi:10.1038/383344a0
42. Arany Z, Huang LE, Eckner R, Bhattacharya S, Jiang C, Goldberg MA, Bunn HF, Livingston DM (1996) An essential role for p300/CBP in the cellular response to hypoxia. Proc Natl Acad Sci USA 93(23):12969–12973
43. Kallio PJ, Okamoto K, O'Brien S, Carrero P, Makino Y, Tanaka H, Poellinger L (1998) Signal transduction in hypoxic cells: inducible nuclear translocation and recruitment of the CBP/p300 coactivator by the hypoxia-inducible factor-1alpha. EMBO J 17(22):6573–6586. doi:10.1093/emboj/17.22.6573
44. Pao GM, Janknecht R, Ruffner H, Hunter T, Verma IM (2000) CBP/p300 interact with and function as transcriptional coactivators of BRCA1. Proc Natl Acad Sci USA 97(3):1020–1025
45. Janknecht R, Nordheim A (1996) MAP kinase-dependent transcriptional coactivation by Elk-1 and its cofactor CBP. Biochem Biophys Res Commun 228(3):831–837. doi:10.1006/bbrc.1996.1740
46. Feng XH, Zhang Y, Wu RY, Derynck R (1998) The tumor suppressor Smad4/DPC4 and transcriptional adaptor CBP/p300 are coactivators for smad3 in TGF-beta-induced transcriptional activation. Genes Dev 12(14):2153–2163
47. Kitabayashi I, Yokoyama A, Shimizu K, Ohki M (1998) Interaction and functional cooperation of the leukemia-associated factors AML1 and p300 in myeloid cell differentiation. EMBO J 17(11):2994–3004. doi:10.1093/emboj/17.11.2994
48. Ait-Si-Ali S, Polesskaya A, Filleur S, Ferreira R, Duquet A, Robin P, Vervish A, Trouche D, Cabon F, Harel-Bellan A (2000) CBP/p300 histone acetyl-transferase activity is important for the G1/S transition. Oncogene 19(20):2430–2437. doi:10.1038/sj.onc.1203562
49. Denis CM, Chitayat S, Plevin MJ, Wang F, Thompson P, Liu S, Spencer HL, Ikura M, Lebrun DP, Smith SP (2012) Structural basis of CBP/p300 recruitment in leukemia induction by E2A-PBX1. Blood 120(19):3968–3977. doi:10.1182/blood-2012-02-411397
50. Teufel DP, Freund SM, Bycroft M, Fersht AR (2007) Four domains of p300 each bind tightly to a sequence spanning both transactivation subdomains of p53. Proc Natl Acad Sci USA 104(17):7009–7014. doi:10.1073/pnas.0702010104
51. Wang F, Marshall CB, Yamamoto K, Li GY, Gasmi-Seabrook GM, Okada H, Mak TW, Ikura M (2012) Structures of KIX domain of CBP in complex with two FOXO3a transactivation domains reveal promiscuity and plasticity in coactivator recruitment. Proc Natl Acad Sci USA 109(16):6078–6083. doi:10.1073/pnas.1119073109
52. Chakravarti D, LaMorte VJ, Nelson MC, Nakajima T, Schulman IG, Juguilon H, Montminy M, Evans RM (1996) Role of CBP/P300 in nuclear receptor signalling. Nature 383(6595):99–103. doi:10.1038/383099a0
53. Fronsdal K, Engedal N, Slagsvold T, Saatcioglu F (1998) CREB binding protein is a coactivator for the androgen receptor and mediates cross-talk with AP-1. J Biol Chem 273(48):31853–31859
54. Hanstein B, Eckner R, DiRenzo J, Halachmi S, Liu H, Searcy B, Kurokawa R, Brown M (1996) p300 is a component of an estrogen receptor coactivator complex. Proc Natl Acad Sci USA 93(21):11540–11545
55. Kee BL, Arias J, Montminy MR (1996) Adaptor-mediated recruitment of RNA polymerase II to a signal-dependent activator. J Biol Chem 271(5):2373–2375
56. Nakajima T, Uchida C, Anderson SF, Lee CG, Hurwitz J, Parvin JD, Montminy M (1997) RNA helicase A mediates association of CBP with RNA polymerase II. Cell 90(6):1107–1112. doi:S0092-8674(00)80376-1
57. Cho H, Orphanides G, Sun X, Yang XJ, Ogryzko V, Lees E, Nakatani Y, Reinberg D (1998) A human RNA polymerase II complex containing factors that modify chromatin structure. Mol Cell Biol 18(9):5355–5363
58. Kim TK, Kim TH, Maniatis T (1998) Efficient recruitment of TFIIB and CBP-RNA polymerase II holoenzyme by an interferon-beta enhanceosome in vitro. Proc Natl Acad Sci USA 95(21):12191–12196
59. Swope DL, Mueller CL, Chrivia JC (1996) CREB-binding protein activates transcription through multiple domains. J Biol Chem 271(45):28138–28145
60. Felzien LK, Farrell S, Betts JC, Mosavin R, Nabel GJ (1999) Specificity of cyclin E-Cdk2, TFIIB, and E1A interactions with a common domain of the p300 coactivator. Mol Cell Biol 19(6):4241–4246
61. Imhof A, Yang XJ, Ogryzko VV, Nakatani Y, Wolffe AP, Ge H (1997) Acetylation of general transcription factors by histone acetyltransferases. Curr Biol 7(9):689–692. doi:S0960-9822(06)00296-X
62. Nagy Z, Tora L (2007) Distinct GCN5/PCAF-containing complexes function as co-activators and are involved in transcription factor and global histone acetylation. Oncogene 26(37):5341–5357. doi:10.1038/sj.onc.1210604
63. Zeng L, Zhang Q, Gerona-Navarro G, Moshkina N, Zhou MM (2008) Structural basis of site-specific histone recognition by the bromodomains of human coactivators PCAF and CBP/p300. Structure 16(4):643–652. doi:10.1016/j.str.2008.01.010
64. Jin Q, Yu LR, Wang L, Zhang Z, Kasper LH, Lee JE, Wang C, Brindle PK, Dent SY, Ge K (2011) Distinct roles of GCN5/PCAF-mediated H3K9ac and CBP/p300-mediated H3K18/27ac in nuclear receptor transactivation. EMBO J 30(2):249–262. doi:10.1038/emboj.2010.318

65. Blanco JC, Minucci S, Lu J, Yang XJ, Walker KK, Chen H, Evans RM, Nakatani Y, Ozato K (1998) The histone acetylase PCAF is a nuclear receptor coactivator. Genes Dev 12(11):1638–1651
66. Paulson M, Press C, Smith E, Tanese N, Levy DE (2002) IFN-Stimulated transcription through a TBP-free acetyltransferase complex escapes viral shutoff. Nat Cell Biol 4(2):140–147. doi:10.1038/ncb747
67. Yang XJ, Ogryzko VV, Nishikawa J, Howard BH, Nakatani Y (1996) A p300/CBP-associated factor that competes with the adenoviral oncoprotein E1A. Nature 382(6589):319–324. doi:10.1038/382319a0
68. Hosoda H, Kato K, Asano H, Ito M, Kato H, Iwamoto T, Suzuki A, Masushige S, Kida S (2009) CBP/p300 is a cell type-specific modulator of CLOCK/BMAL1-mediated transcription. Mol Brain 2:34. doi:10.1186/1756-6606-2-34
69. Xu W, Edmondson DG, Roth SY (1998) Mammalian GCN5 and P/CAF acetyltransferases have homologous amino-terminal domains important for recognition of nucleosomal substrates. Mol Cell Biol 18(10):5659–5669
70. Kahata K, Hayashi M, Asaka M, Hellman U, Kitagawa H, Yanagisawa J, Kato S, Imamura T, Miyazono K (2004) Regulation of transforming growth factor-beta and bone morphogenetic protein signalling by transcriptional coactivator GCN5. Genes Cells 9(2):143–151. doi:706
71. Phan HM, Xu AW, Coco C, Srajer G, Wyszomierski S, Evrard YA, Eckner R, Dent SY (2005) GCN5 and p300 share essential functions during early embryogenesis. Dev Dyn 233(4):1337–1347. doi:10.1002/dvdy.20445
72. Michael LF, Asahara H, Shulman AI, Kraus WL, Montminy M (2000) The phosphorylation status of a cyclic AMP-responsive activator is modulated via a chromatin-dependent mechanism. Mol Cell Biol 20(5):1596–1603
73. Radhakrishnan I, Perez-Alvarado GC, Parker D, Dyson HJ, Montminy MR, Wright PE (1997) Solution structure of the KIX domain of CBP bound to the transactivation domain of CREB: a model for activator: coactivator interactions. Cell 91(6):741–752. doi:S0092-8674(00)80463-8
74. Sugase K, Dyson HJ, Wright PE (2007) Mechanism of coupled folding and binding of an intrinsically disordered protein. Nature 447(7147):1021–1025. doi:10.1038/nature05858
75. Solt I, Magyar C, Simon I, Tompa P, Fuxreiter M (2006) Phosphorylation-induced transient intrinsic structure in the kinase-inducible domain of CREB facilitates its recognition by the KIX domain of CBP. Proteins 64(3):749–757. doi:10.1002/prot.21032
76. Turjanski AG, Gutkind JS, Best RB, Hummer G (2008) Binding-induced folding of a natively unstructured transcription factor. PLoS Comput Biol 4(4):e1000060. doi:10.1371/journal.pcbi.1000060
77. Zor T, Mayr BM, Dyson HJ, Montminy MR, Wright PE (2002) Roles of phosphorylation and helix propensity in the binding of the KIX domain of CREB-binding protein by constitutive (c-Myb) and inducible (CREB) activators. J Biol Chem 277(44):42241–42248. doi:10.1074/jbc.M207361200
78. Zor T, De Guzman RN, Dyson HJ, Wright PE (2004) Solution structure of the KIX domain of CBP bound to the transactivation domain of c-Myb. J Mol Biol 337(3):521–534. doi:10.1016/j.jmb.2004.01.038
79. Goto NK, Zor T, Martinez-Yamout M, Dyson HJ, Wright PE (2002) Cooperativity in transcription factor binding to the coactivator CREB-binding protein (CBP). The mixed lineage leukemia protein (MLL) activation domain binds to an allosteric site on the KIX domain. J Biol Chem 277(45):43168–43174. doi:10.1074/jbc.M207660200
80. De Guzman RN, Goto NK, Dyson HJ, Wright PE (2006) Structural basis for cooperative transcription factor binding to the CBP coactivator. J Mol Biol 355(5):1005–1013. doi:10.1016/j.jmb.2005.09.059
81. Steegenga WT, van Laar T, Riteco N, Mandarino A, Shvarts A, van der Eb AJ, Jochemsen AG (1996) Adenovirus E1A proteins inhibit activation of transcription by p53. Mol Cell Biol 16(5):2101–2109
82. Scolnick DM, Chehab NH, Stavridi ES, Lien MC, Caruso L, Moran E, Berger SL, Halazonetis TD (1997) CREB-binding protein and p300/CBP-associated factor are transcriptional coactivators of the p53 tumor suppressor protein. Cancer Res 57(17):3693–3696
83. Wang F, Marshall CB, Li GY, Yamamoto K, Mak TW, Ikura M (2009) Synergistic interplay between promoter recognition and CBP/p300 coactivator recruitment by FOXO3a. ACS Chem Biol 4(12):1017–1027. doi:10.1021/cb900190u
84. Lee CW, Arai M, Martinez-Yamout MA, Dyson HJ, Wright PE (2009) Mapping the interactions of the p53 transactivation domain with the KIX domain of CBP. Biochemistry 48(10):2115–2124. doi:10.1021/bi802055v
85. Cook PR, Polakowski N, Lemasson I (2011) HTLV-1 HBZ protein deregulates interactions between cellular factors and the KIX domain of p300/CBP. J Mol Biol 409(3):384–398. doi:10.1016/j.jmb.2011.04.003
86. Campbell KM, Lumb KJ (2002) Structurally distinct modes of recognition of the KIX domain of CBP by Jun and CREB. Biochemistry 41(47):13956–13964. doi:bi026222m
87. Lee YH, Bedford MT, Stallcup MR (2011) Regulated recruitment of tumor suppressor BRCA1 to the p21 gene by coactivator methylation. Genes Dev 25(2):176–188. doi:10.1101/gad.1975811
88. Bayly R, Chuen L, Currie RA, Hyndman BD, Casselman R, Blobel GA, LeBrun DP (2004) E2A-PBX1 interacts directly with the KIX domain of CBP/p300 in the induction of proliferation in primary hematopoietic cells. J Biol Chem 279(53):55362–55371. doi:10.1074/jbc.M408654200
89. Hyndman BD, Thompson P, Bayly R, Cote GP (1819) Lebrun DP (2012) E2A proteins enhance the histone acetyltransferase activity of the transcriptional co-activators CBP and p300. Biochim Biophys Acta 5:446–453. doi:10.1016/j.bbagrm.2012.02.009
90. Ramirez JA, Nyborg JK (2007) Molecular characterization of HTLV-1 Tax interaction with the KIX domain of CBP/p300. J Mol Biol 372(4):958–969. doi:10.1016/j.jmb.2007.06.062
91. Oliner JD, Andresen JM, Hansen SK, Zhou S, Tjian R (1996) SREBP transcriptional activity is mediated through an interaction with the CREB-binding protein. Genes Dev 10(22):2903–2911
92. Plevin MJ, Mills MM, Ikura M (2005) The LxxLL motif: a multifunctional binding sequence in transcriptional regulation. Trends Biochem Sci 30(2):66–69. doi:10.1016/j.tibs.2004.12.001
93. De Guzman RN, Wojciak JM, Martinez-Yamout MA, Dyson HJ, Wright PE (2005) CBP/p300 TAZ1 domain forms a structured scaffold for ligand binding. Biochemistry 44(2):490–497. doi:10.1021/bi048161t
94. Legge GB, Martinez-Yamout MA, Hambly DM, Trinh T, Lee BM, Dyson HJ, Wright PE (2004) ZZ domain of CBP: an unusual zinc finger fold in a protein interaction module. J Mol Biol 343(4):1081–1093. doi:10.1016/j.jmb.2004.08.087
95. Miller M, Dauter Z, Cherry S, Tropea JE, Wlodawer A (2009) Structure of the Taz2 domain of p300: insights into ligand binding. Acta Crystallogr D Biol Crystallogr 65(Pt 12):1301–1308. doi:10.1107/S0907444909040153
96. Kalkhoven E, Teunissen H, Houweling A, Verrijzer CP, Zantema A (2002) The PHD type zinc finger is an integral part of the CBP acetyltransferase domain. Mol Cell Biol 22(7):1961–1970
97. Zeng L, Yap KL, Ivanov AV, Wang X, Mujtaba S, Plotnikova O, Rauscher FJ 3rd, Zhou MM (2008) Structural insights into human

KAP1 PHD finger-bromodomain and its role in gene silencing. Nat Struct Mol Biol 15(6):626–633. doi:10.1038/nsmb.1416
98. Lallous N, Legrand P, McEwen AG, Ramon-Maiques S, Samama JP, Birck C (2011) The PHD finger of human UHRF1 reveals a new subgroup of unmethylated histone H3 tail readers. PLoS ONE 6(11):e27599. doi:10.1371/journal.pone.0027599
99. Ruas JL, Poellinger L, Pereira T (2005) Role of CBP in regulating HIF-1-mediated activation of transcription. J Cell Sci 118(Pt 2):301–311. doi:10.1242/jcs.01617
100. Ferreon JC, Lee CW, Arai M, Martinez-Yamout MA, Dyson HJ, Wright PE (2009) Cooperative regulation of p53 by modulation of ternary complex formation with CBP/p300 and HDM2. Proc Natl Acad Sci USA 106(16):6591–6596. doi:10.1073/pnas.0811023106
101. Feng H, Jenkins LM, Durell SR, Hayashi R, Mazur SJ, Cherry S, Tropea JE, Miller M, Wlodawer A, Appella E, Bai Y (2009) Structural basis for p300 Taz2-p53 TAD1 binding and modulation by phosphorylation. Structure 17(2):202–210. doi:10.1016/j.str.2008.12.009
102. Jenkins LM, Yamaguchi H, Hayashi R, Cherry S, Tropea JE, Miller M, Wlodawer A, Appella E, Mazur SJ (2009) Two distinct motifs within the p53 transactivation domain bind to the Taz2 domain of p300 and are differentially affected by phosphorylation. Biochemistry 48(6):1244–1255. doi:10.1021/bi801716h
103. Arai M, Ferreon JC, Wright PE (2012) Quantitative analysis of multisite protein-ligand interactions by NMR: binding of intrinsically disordered p53 transactivation subdomains with the TAZ2 domain of CBP. J Am Chem Soc 134(8):3792–3803. doi:10.1021/ja209936u
104. Dames SA, Martinez-Yamout M, De Guzman RN, Dyson HJ, Wright PE (2002) Structural basis for Hif-1 alpha/CBP recognition in the cellular hypoxic response. Proc Natl Acad Sci USA 99(8):5271–5276. doi:10.1073/pnas.082121399
105. Yin Z, Haynie J, Yang X, Han B, Kiatchoosakun S, Restivo J, Yuan S, Prabhakar NR, Herrup K, Conlon RA, Hoit BD, Watanabe M, Yang YC (2002) The essential role of Cited2, a negative regulator for HIF-1alpha, in heart development and neurulation. Proc Natl Acad Sci USA 99(16):10488–10493. doi:10.1073/pnas.162371799
106. De Guzman RN, Martinez-Yamout MA, Dyson HJ, Wright PE (2004) Interaction of the TAZ1 domain of the CREB-binding protein with the activation domain of CITED2: regulation by competition between intrinsically unstructured ligands for non-identical binding sites. J Biol Chem 279(4):3042–3049. doi:10.1074/jbc.M310348200
107. Freedman SJ, Sun ZY, Kung AL, France DS, Wagner G, Eck MJ (2003) Structural basis for negative regulation of hypoxia-inducible factor-1alpha by CITED2. Nat Struct Biol 10(7):504–512. doi:10.1038/nsb936
108. O'Connor MJ, Zimmermann H, Nielsen S, Bernard HU, Kouzarides T (1999) Characterization of an E1A-CBP interaction defines a novel transcriptional adapter motif (TRAM) in CBP/p300. J Virol 73(5):3574–3581
109. Kurokawa R, Kalafus D, Ogliastro MH, Kioussi C, Xu L, Torchia J, Rosenfeld MG, Glass CK (1998) Differential use of CREB binding protein-coactivator complexes. Science 279(5351):700–703
110. Fax P, Lipinski KS, Esche H, Brockmann D (2000) cAMP-independent activation of the adenovirus type 12 E2 promoter correlates with the recruitment of CREB-1/ATF-1, E1A(12S), and CBP to the E2-CRE. J Biol Chem 275(12):8911–8920
111. Ferreon JC, Martinez-Yamout MA, Dyson HJ, Wright PE (2009) Structural basis for subversion of cellular control mechanisms by the adenoviral E1A oncoprotein. Proc Natl Acad Sci USA 106(32):13260–13265. doi:10.1073/pnas.0906770106
112. Wojciak JM, Martinez-Yamout MA, Dyson HJ, Wright PE (2009) Structural basis for recruitment of CBP/p300 coactivators by STAT1 and STAT2 transactivation domains. EMBO J 28(7):948–958. doi:10.1038/emboj.2009.30
113. McKinsey TA, Zhang CL, Olson EN (2002) MEF2: a calcium-dependent regulator of cell division, differentiation and death. Trends Biochem Sci 27(1):40–47. doi:S0968-0004(01)02031-X
114. Sartorelli V, Huang J, Hamamori Y, Kedes L (1997) Molecular mechanisms of myogenic coactivation by p300: direct interaction with the activation domain of MyoD and with the MADS box of MEF2C. Mol Cell Biol 17(2):1010–1026
115. Youn HD, Chatila TA, Liu JO (2000) Integration of calcineurin and MEF2 signals by the coactivator p300 during T-cell apoptosis. EMBO J 19(16):4323–4331. doi:10.1093/emboj/19.16.4323
116. Slepak TI, Webster KA, Zang J, Prentice H, O'Dowd A, Hicks MN, Bishopric NH (2001) Control of cardiac-specific transcription by p300 through myocyte enhancer factor-2D. J Biol Chem 276(10):7575–7585. doi:10.1074/jbc.M004625200
117. He J, Ye J, Cai Y, Riquelme C, Liu JO, Liu X, Han A, Chen L (2011) Structure of p300 bound to MEF2 on DNA reveals a mechanism of enhanceosome assembly. Nucleic Acids Res 39(10):4464–4474. doi:10.1093/nar/gkr030
118. Qin BY, Liu C, Srinath H, Lam SS, Correia JJ, Derynck R, Lin K (2005) Crystal structure of IRF-3 in complex with CBP. Structure 13(9):1269–1277. doi:10.1016/j.str.2005.06.011
119. Lee CW, Martinez-Yamout MA, Dyson HJ, Wright PE (2010) Structure of the p53 transactivation domain in complex with the nuclear receptor coactivator binding domain of CREB binding protein. Biochemistry 49(46):9964–9971. doi:10.1021/bi1012996
120. Chen D, Huang SM, Stallcup MR (2000) Synergistic, p160 coactivator-dependent enhancement of estrogen receptor function by CARM1 and p300. J Biol Chem 275(52):40810–40816. doi:10.1074/jbc.M005459200
121. Demarest SJ, Deechongkit S, Dyson HJ, Evans RM, Wright PE (2004) Packing, specificity, and mutability at the binding interface between the p160 coactivator and CREB-binding protein. Protein Sci 13(1):203–210. doi:10.1110/ps.03366504
122. Kjaergaard M, Teilum K, Poulsen FM (2010) Conformational selection in the molten globule state of the nuclear coactivator binding domain of CBP. Proc Natl Acad Sci USA 107(28):12535–12540. doi:10.1073/pnas.1001693107
123. Hammes GG, Chang YC, Oas TG (2009) Conformational selection or induced fit: a flux description of reaction mechanism. Proc Natl Acad Sci USA 106(33):13737–13741. doi:10.1073/pnas.0907195106
124. Moras D, Gronemeyer H (1998) The nuclear receptor ligand-binding domain: structure and function. Curr Opin Cell Biol 10(3):384–391. doi:S0955-0674(98)80015-X
125. Heery DM, Kalkhoven E, Hoare S, Parker MG (1997) A signature motif in transcriptional co-activators mediates binding to nuclear receptors. Nature 387(6634):733–736. doi:10.1038/42750
126. Dyson HJ, Wright PE (2005) Intrinsically unstructured proteins and their functions. Nat Rev Mol Cell Biol 6(3):197–208. doi:10.1038/nrm1589
127. Mittag T, Kay LE, Forman-Kay JD (2010) Protein dynamics and conformational disorder in molecular recognition. J Mol Recognit 23(2):105–116. doi:10.1002/jmr.961
128. Lee CW, Ferreon JC, Ferreon AC, Arai M, Wright PE (2010) Graded enhancement of p53 binding to CREB-binding protein (CBP) by multisite phosphorylation. Proc Natl Acad Sci USA 107(45):19290–19295. doi:10.1073/pnas.1013078107
129. Mas C, Lussier-Price M, Soni S, Morse T, Arseneault G, Di Lello P, Lafrance-Vanasse J, Bieker JJ, Omichinski JG (2011) Structural and functional characterization of an atypical activation

domain in erythroid Kruppel-like factor (EKLF). Proc Natl Acad Sci USA 108(26):10484–10489. doi:10.1073/pnas.1017029108
130. Wang F, Marshall CB, Yamamoto K, Li GY, Plevin MJ, You H, Mak TW, Ikura M (2008) Biochemical and structural characterization of an intramolecular interaction in FOXO3a and its binding with p53. J Mol Biol 384(3):590–603. doi:10.1016/j.jmb.2008.09.025
131. You H, Yamamoto K, Mak TW (2006) Regulation of transactivation-independent proapoptotic activity of p53 by FOXO3a. Proc Natl Acad Sci USA 103(24):9051–9056. doi:10.1073/pnas.0600889103
132. Renault VM, Thekkat PU, Hoang KL, White JL, Brady CA, Kenzelmann Broz D, Venturelli OS, Johnson TM, Oskoui PR, Xuan Z, Santo EE, Zhang MQ, Vogel H, Attardi LD, Brunet A (2011) The pro-longevity gene FoxO3 is a direct target of the p53 tumor suppressor. Oncogene 30(29):3207–3221. doi:10.1038/onc.2011.35
133. Shuai K (2000) Modulation of STAT signaling by STAT-interacting proteins. Oncogene 19(21):2638–2644. doi:10.1038/sj.onc.1203522
134. Seoane J, Le HV, Shen L, Anderson SA, Massague J (2004) Integration of Smad and forkhead pathways in the control of neuroepithelial and glioblastoma cell proliferation. Cell 117(2):211–223. doi:S0092867404002983
135. Gotea V, Visel A, Westlund JM, Nobrega MA, Pennacchio LA, Ovcharenko I (2010) Homotypic clusters of transcription factor binding sites are a key component of human promoters and enhancers. Genome Res 20(5):565–577. doi:gr.10.1101/gr.104471.109
136. Bakker WJ, Harris IS, Mak TW (2007) FOXO3a is activated in response to hypoxic stress and inhibits HIF1-induced apoptosis via regulation of CITED2. Mol Cell 28(6):941–953. doi:10.1016/j.molcel.2007.10.035
137. Emerling BM, Weinberg F, Liu JL, Mak TW, Chandel NS (2008) PTEN regulates p300-dependent hypoxia-inducible factor 1 transcriptional activity through Forkhead transcription factor 3a (FOXO3a). Proc Natl Acad Sci USA 105(7):2622–2627. doi:10.1073/pnas.0706790105
138. Xie H, Vucetic S, Iakoucheva LM, Oldfield CJ, Dunker AK, Obradovic Z, Uversky VN (2007) Functional anthology of intrinsic disorder. 3. Ligands, post-translational modifications, and diseases associated with intrinsically disordered proteins. J Proteome Res 6(5):1917–1932. doi:10.1021/pr060394e
139. Sun P, Enslen H, Myung PS, Maurer RA (1994) Differential activation of CREB by Ca^{2+}/calmodulin-dependent protein kinases type II and type IV involves phosphorylation of a site that negatively regulates activity. Genes Dev 8(21):2527–2539
140. Shi Y, Venkataraman SL, Dodson GE, Mabb AM, LeBlanc S, Tibbetts RS (2004) Direct regulation of CREB transcriptional activity by ATM in response to genotoxic stress. Proc Natl Acad Sci USA 101(16):5898–5903. doi:10.1073/pnas.0307718101
141. Shanware NP, Trinh AT, Williams LM, Tibbetts RS (2007) Coregulated ataxia telangiectasia-mutated and casein kinase sites modulate cAMP-response element-binding protein-coactivator interactions in response to DNA damage. J Biol Chem 282(9):6283–6291. doi:10.1074/jbc.M610674200
142. Altarejos JY, Montminy M (2011) CREB and the CRTC co-activators: sensors for hormonal and metabolic signals. Nat Rev Mol Cell Biol 12(3):141–151. doi:10.1038/nrm3072
143. Lambert PF, Kashanchi F, Radonovich MF, Shiekhattar R, Brady JN (1998) Phosphorylation of p53 serine 15 increases interaction with CBP. J Biol Chem 273(49):33048–33053
144. Teufel DP, Bycroft M, Fersht AR (2009) Regulation by phosphorylation of the relative affinities of the N-terminal transactivation domains of p53 for p300 domains and Mdm2. Oncogene 28(20):2112–2118. doi:10.1038/onc.2009.71
145. Cho H, Ahn DR, Park H, Yang EG (2007) Modulation of p300 binding by posttranslational modifications of the C-terminal activation domain of hypoxia-inducible factor-1alpha. FEBS Lett 581(8):1542–1548. doi:10.1016/j.febslet.2007.03.015
146. Zanger K, Cohen LE, Hashimoto K, Radovick S, Wondisford FE (1999) A novel mechanism for cyclic adenosine 3′,5′-monophosphate regulation of gene expression by CREB-binding protein. Mol Endocrinol 13(2):268–275
147. Zhou XY, Shibusawa N, Naik K, Porras D, Temple K, Ou H, Kaihara K, Roe MW, Brady MJ, Wondisford FE (2004) Insulin regulation of hepatic gluconeogenesis through phosphorylation of CREB-binding protein. Nat Med 10(6):633–637. doi:10.1038/nm1050
148. Zanger K, Radovick S, Wondisford FE (2001) CREB binding protein recruitment to the transcription complex requires growth factor-dependent phosphorylation of its GF box. Mol Cell 7(3):551–558. doi:S1097-2765(01)00202-7
149. Banerjee T, Chakravarti D (2011) A peek into the complex realm of histone phosphorylation. Mol Cell Biol 31(24):4858–4873. doi:10.1128/MCB.05631-11
150. Cheung P, Lau P (2005) Epigenetic regulation by histone methylation and histone variants. Mol Endocrinol 19(3):563–573. doi:10.1210/me.2004-0496
151. Weake VM, Workman JL (2008) Histone ubiquitination: triggering gene activity. Mol Cell 29(6):653–663. doi:10.1016/j.molcel.2008.02.014
152. Shiio Y, Eisenman RN (2003) Histone sumoylation is associated with transcriptional repression. Proc Natl Acad Sci USA 100(23):13225–13230. doi:10.1073/pnas.1735528100
153. Shahbazian MD, Grunstein M (2007) Functions of site-specific histone acetylation and deacetylation. Annu Rev Biochem 76:75–100. doi:10.1146/annurev.biochem.76.052705.162114
154. Jenuwein T, Allis CD (2001) Translating the histone code. Science 293(5532):1074–1080. doi:10.1126/science.1063127
155. Wang GG, Allis CD, Chi P (2007) Chromatin remodeling and cancer, Part I: covalent histone modifications. Trends Mol Med 13(9):363–372. doi:10.1016/j.molmed.2007.07.003
156. Gorisch SM, Wachsmuth M, Toth KF, Lichter P, Rippe K (2005) Histone acetylation increases chromatin accessibility. J Cell Sci 118(Pt 24):5825–5834. doi:10.1242/jcs.02689
157. Schiltz RL, Mizzen CA, Vassilev A, Cook RG, Allis CD, Nakatani Y (1999) Overlapping but distinct patterns of histone acetylation by the human coactivators p300 and PCAF within nucleosomal substrates. J Biol Chem 274(3):1189–1192
158. Das C, Lucia MS, Hansen KC, Tyler JK (2009) CBP/p300-mediated acetylation of histone H3 on lysine 56. Nature 459(7243):113–117. doi:10.1038/nature07861
159. Liu X, Wang L, Zhao K, Thompson PR, Hwang Y, Marmorstein R, Cole PA (2008) The structural basis of protein acetylation by the p300/CBP transcriptional coactivator. Nature 451(7180):846–850. doi:10.1038/nature06546
160. Wang L, Tang Y, Cole PA, Marmorstein R (2008) Structure and chemistry of the p300/CBP and Rtt109 histone acetyltransferases: implications for histone acetyltransferase evolution and function. Curr Opin Struct Biol 18(6):741–747. doi:10.1016/j.sbi.2008.09.004
161. Chakravarti D, Ogryzko V, Kao HY, Nash A, Chen H, Nakatani Y, Evans RM (1999) A viral mechanism for inhibition of p300 and PCAF acetyltransferase activity. Cell 96(3):393–403. doi:S0092-8674(00)80552-8
162. MacLellan WR, Xiao G, Abdellatif M, Schneider MD (2000) A novel Rb- and p300-binding protein inhibits transactivation by MyoD. Mol Cell Biol 20(23):8903–8915
163. Miyake S, Sellers WR, Safran M, Li X, Zhao W, Grossman SR, Gan J, DeCaprio JA, Adams PD, Kaelin WG Jr (2000) Cells degrade a novel inhibitor of differentiation with

E1A-like properties upon exiting the cell cycle. Mol Cell Biol 20(23):8889–8902
164. Liu R, Lei JX, Luo C, Lan X, Chi L, Deng P, Lei S, Ghribi O, Liu QY (2012) Increased EID1 nuclear translocation impairs synaptic plasticity and memory function associated with pathogenesis of Alzheimer's disease. Neurobiol Dis 45(3):902–912. doi:10.1016/j.nbd.2011.12.007
165. Mujtaba S, He Y, Zeng L, Yan S, Plotnikova O, Sachchidanand, Sanchez R, Zeleznik-Le NJ, Ronai Z, Zhou MM (2004) Structural mechanism of the bromodomain of the coactivator CBP in p53 transcriptional activation. Mol Cell 13(2):251–263. doi:S1097276503005288
166. Gu W, Shi XL, Roeder RG (1997) Synergistic activation of transcription by CBP and p53. Nature 387(6635):819–823. doi:10.1038/42972
167. Ma K, Chan JK, Zhu G, Wu Z (2005) Myocyte enhancer factor 2 acetylation by p300 enhances its DNA binding activity, transcriptional activity, and myogenic differentiation. Mol Cell Biol 25(9):3575–3582. doi:10.1128/MCB.25.9.3575-3582.2005
168. Tu AW, Luo K (2007) Acetylation of Smad2 by the co-activator p300 regulates activin and transforming growth factor beta response. J Biol Chem 282(29):21187–21196. doi:10.1074/jbc.M700085200
169. Lu Q, Hutchins AE, Doyle CM, Lundblad JR, Kwok RP (2003) Acetylation of cAMP-responsive element-binding protein (CREB) by CREB-binding protein enhances CREB-dependent transcription. J Biol Chem 278(18):15727–15734. doi:10.1074/jbc.M300546200
170. Hyndman BD, Thompson P, Denis CM, Chitayat S, Bayly R, Smith SP (1819) Lebrun DP (2012) Mapping acetylation sites in E2A identifies a conserved lysine residue in activation domain 1 that promotes CBP/p300 recruitment and transcriptional activation. Biochim Biophys Acta 5:375–381. doi:10.1016/j.bbagrm.2011.11.013
171. van der Heide LP, Smidt MP (2005) Regulation of FoxO activity by CBP/p300-mediated acetylation. Trends Biochem Sci 30(2):81–86. doi:10.1016/j.tibs.2004.12.002
172. Perrot V, Rechler MM (2005) The coactivator p300 directly acetylates the forkhead transcription factor Foxo1 and stimulates Foxo1-induced transcription. Mol Endocrinol 19(9):2283–2298. doi:10.1210/me.2004-0292
173. Waltzer L, Bienz M (1998) Drosophila CBP represses the transcription factor TCF to antagonize Wingless signalling. Nature 395(6701):521–525. doi:10.1038/26785
174. Rubinstein JH, Taybi H (1963) Broad thumbs and toes and facial abnormalities. A possible mental retardation syndrome. Am J Dis Child 105:588–608
175. Blough RI, Petrij F, Dauwerse JG, Milatovich-Cherry A, Weiss L, Saal HM, Rubinstein JH (2000) Variation in microdeletions of the cyclic AMP-responsive element-binding protein gene at chromosome band 16p13.3 in the Rubinstein-Taybi syndrome. Am J Med Genet 90(1):29–34. doi:10.1002/(SICI)1096-8628(20000103)90:1<29:AID-AJMG6>3.0.CO;2-Z
176. Petrij F, Dorsman JC, Dauwerse HG, Giles RH, Peeters T, Hennekam RC, Breuning MH, Peters DJ (2000) Rubinstein-Taybi syndrome caused by a De Novo reciprocal translocation t(2;16)(q36.3;p13.3). Am J Med Genet 92(1):47–52. doi:10.1002/(SICI)1096-8628(20000501)92:1<47:AID-AJMG8>3.0.CO;2-H
177. Kung AL, Rebel VI, Bronson RT, Ch'ng LE, Sieff CA, Livingston DM, Yao TP (2000) Gene dose-dependent control of hematopoiesis and hematologic tumor suppression by CBP. Genes Dev 14(3):272–277
178. Kimbrel EA, Lemieux ME, Xia X, Davis TN, Rebel VI, Kung AL (2009) Systematic in vivo structure-function analysis of p300 in hematopoiesis. Blood 114(23):4804–4812. doi:10.1182/blood-2009-04-217794
179. Morin RD, Mendez-Lago M, Mungall AJ, Goya R, Mungall KL, Corbett RD, Johnson NA, Severson TM, Chiu R, Field M, Jackman S, Krzywinski M, Scott DW, Trinh DL, Tamura-Wells J, Li S, Firme MR, Rogic S, Griffith M, Chan S, Yakovenko O, Meyer IM, Zhao EY, Smailus D, Moksa M, Chittaranjan S, Rimsza L, Brooks-Wilson A, Spinelli JJ, Ben-Neriah S, Meissner B, Woolcock B, Boyle M, McDonald H, Tam A, Zhao Y, Delaney A, Zeng T, Tse K, Butterfield Y, Birol I, Holt R, Schein J, Horsman DE, Moore R, Jones SJ, Connors JM, Hirst M, Gascoyne RD, Marra MA (2011) Frequent mutation of histone-modifying genes in non-Hodgkin lymphoma. Nature 476(7360):298–303. doi:10.1038/nature10351
180. Borrow J, Stanton VP Jr, Andresen JM, Becher R, Behm FG, Chaganti RS, Civin CI, Disteche C, Dube I, Frischauf AM, Horsman D, Mitelman F, Volinia S, Watmore AE, Housman DE (1996) The translocation t(8;16)(p11;p13) of acute myeloid leukaemia fuses a putative acetyltransferase to the CREB-binding protein. Nat Genet 14(1):33–41. doi:10.1038/ng0996-33
181. Chaffanet M, Gressin L, Preudhomme C, Soenen-Cornu V, Birnbaum D, Pebusque MJ (2000) MOZ is fused to p300 in an acute monocytic leukemia with t(8;22). Genes Chromosomes Cancer 28(2):138–144. doi:10.1002/(SICI)1098-2264(200006)28:2<138:AID-GCC2>3.0.CO;2-2
182. Satake N, Ishida Y, Otoh Y, Hinohara S, Kobayashi H, Sakashita A, Maseki N, Kaneko Y (1997) Novel MLL-CBP fusion transcript in therapy-related chronic myelomonocytic leukemia with a t(11;16)(q23;p13) chromosome translocation. Genes Chromosomes Cancer 20(1):60–63. doi:10.1002/(SICI)1098-2264(199709)20:1<60:AID-GCC9>3.0.CO;2-7
183. Sobulo OM, Borrow J, Tomek R, Reshmi S, Harden A, Schlegelberger B, Housman D, Doggett NA, Rowley JD, Zeleznik-Le NJ (1997) 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 94(16):8732–8737
184. Rowley JD, Reshmi S, Sobulo O, Musvee T, Anastasi J, Raimondi S, Schneider NR, Barredo JC, Cantu ES, Schlegelberger B, Behm F, Doggett NA, Borrow J, Zeleznik-Le N (1997) All patients with the T(11;16)(q23;p13.3) that involves MLL and CBP have treatment-related hematologic disorders. Blood 90(2):535–541
185. Taki T, Sako M, Tsuchida M, Hayashi Y (1997) The t(11;16)(q23;p13) translocation in myelodysplastic syndrome fuses the MLL gene to the CBP gene. Blood 89(11):3945–3950
186. Lavau C, Du C, Thirman M, Zeleznik-Le N (2000) Chromatin-related properties of CBP fused to MLL generate a myelodysplastic-like syndrome that evolves into myeloid leukemia. EMBO J 19(17):4655–4664. doi:10.1093/emboj/19.17.4655
187. Debes JD, Sebo TJ, Lohse CM, Murphy LM, Haugen DA, Tindall DJ (2003) p300 in prostate cancer proliferation and progression. Cancer Res 63(22):7638–7640
188. Ianculescu I, Wu DY, Siegmund KD, Stallcup MR (2012) Selective roles for cAMP response element-binding protein binding protein and p300 protein as coregulators for androgen-regulated gene expression in advanced prostate cancer cells. J Biol Chem 287(6):4000–4013. doi:10.1074/jbc.M111.300194
189. Ionov Y, Matsui S, Cowell JK (2004) 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 101(5):1273–1278. doi:10.1073/pnas.0307276101
190. Takeuchi A, Shiota M, Tatsugami K, Yokomizo A, Tanaka S, Kuroiwa K, Eto M, Naito S (2012) p300 mediates cellular resistance to doxorubicin in bladder cancer. Mol Med Rep 5(1):173–176. doi:10.3892/mmr.2011.593
191. Hao S, He W, Li Y, Ding H, Hou Y, Nie J, Hou FF, Kahn M, Liu Y (2011) Targeted inhibition of beta-catenin/CBP

signaling ameliorates renal interstitial fibrosis. J Am Soc Nephrol 22(9):1642–1653. doi:10.1681/ASN.2010101079
192. Zhou B, Liu Y, Kahn M, Ann DK, Han A, Wang H, Nguyen C, Flodby P, Zhong Q, Krishnaveni MS, Liebler JM, Minoo P, Crandall ED, Borok Z (2012) Interactions between beta-catenin and transforming growth factor-beta signaling pathways mediate epithelial-mesenchymal transition and are dependent on the transcriptional co-activator cAMP-response element-binding protein (CREB)-binding protein (CBP). J Biol Chem 287(10):7026–7038. doi:10.1074/jbc.M111.276311
193. Kim YM, Ma H, Oehler VG, Gang EJ, Nguyen C, Masiello D, Liu H, Zhao Y, Radich J, Kahn M (2011) The gamma catenin/CBP complex maintains survivin transcription in beta-catenin deficient/depleted cancer cells. Curr Cancer Drug Targets 11(2):213–225. doi:EPub-Abstract-CCDT-97
194. Marzio G, Tyagi M, Gutierrez MI, Giacca M (1998) HIV-1 tat transactivator recruits p300 and CREB-binding protein histone acetyltransferases to the viral promoter. Proc Natl Acad Sci USA 95(23):13519–13524
195. Caccamo A, Maldonado MA, Bokov AF, Majumder S, Oddo S (2010) CBP gene transfer increases BDNF levels and ameliorates learning and memory deficits in a mouse model of Alzheimer's disease. Proc Natl Acad Sci USA 107(52):22687–22692. doi:10.1073/pnas.1012851108
196. Stanojevic V, Habener JF, Thomas MK (2004) Pancreas duodenum homeobox-1 transcriptional activation requires interactions with p300. Endocrinology 145(6):2918–2928. doi:10.1210/en.2003-1188
197. Chen G, Zhu J, Lv T, Wu G, Sun H, Huang X, Tian J (2009) Spatiotemporal expression of histone acetyltransferases, p300 and CBP, in developing embryonic hearts. J Biomed Sci 16:24. doi:10.1186/1423-0127-16-24
198. Wei JQ, Shehadeh LA, Mitrani JM, Pessanha M, Slepak TI, Webster KA, Bishopric NH (2008) Quantitative control of adaptive cardiac hypertrophy by acetyltransferase p300. Circulation 118(9):934–946. doi:10.1161/CIRCULATIONAHA.107.760488
199. Lee LW, Mapp AK (2010) Transcriptional switches: chemical approaches to gene regulation. J Biol Chem 285(15):11033–11038. doi:10.1074/jbc.R109.075044
200. Balasubramanyam K, Varier RA, Altaf M, Swaminathan V, Siddappa NB, Ranga U, Kundu TK (2004) Curcumin, a novel p300/CREB-binding protein-specific inhibitor of acetyltransferase, represses the acetylation of histone/nonhistone proteins and histone acetyltransferase-dependent chromatin transcription. J Biol Chem 279(49):51163–51171. doi:10.1074/jbc.M409024200
201. Zhou H, Beevers CS, Huang S (2011) The targets of curcumin. Curr Drug Targets 12(3):332–347. doi:BSP/CDT/E-Pub/00185
202. Mantelingu K, Reddy BA, Swaminathan V, Kishore AH, Siddappa NB, Kumar GV, Nagashankar G, Natesh N, Roy S, Sadhale PP, Ranga U, Narayana C, Kundu TK (2007) Specific inhibition of p300-HAT alters global gene expression and represses HIV replication. Chem Biol 14(6):645–657. doi:10.1016/j.chembiol.2007.04.011
203. Arif M, Pradhan SK, Thanuja GR, Vedamurthy BM, Agrawal S, Dasgupta D, Kundu TK (2009) Mechanism of p300 specific histone acetyltransferase inhibition by small molecules. J Med Chem 52(2):267–277. doi:10.1021/jm800657z
204. Santer FR, Hoschele PP, Oh SJ, Erb HH, Bouchal J, Cavarretta IT, Parson W, Meyers DJ, Cole PA, Culig Z (2011) Inhibition of the acetyltransferases p300 and CBP reveals a targetable function for p300 in the survival and invasion pathways of prostate cancer cell lines. Mol Cancer Ther 10(9):1644–1655. doi:10.1158/1535-7163.MCT-11-0182
205. Filippakopoulos P, Knapp S (2012) The bromodomain interaction module. FEBS Lett 586(17):2692–2704. doi:10.1016/j.febslet.2012.04.045
206. Filippakopoulos P, Picaud S, Mangos M, Keates T, Lambert JP, Barsyte-Lovejoy D, Felletar I, Volkmer R, Muller S, Pawson T, Gingras AC, Arrowsmith CH, Knapp S (2012) Histone recognition and large-scale structural analysis of the human bromodomain family. Cell 149(1):214–231. doi:10.1016/j.cell.2012.02.013
207. Chen J, Ghazawi FM, Li Q (2010) Interplay of bromodomain and histone acetylation in the regulation of p300-dependent genes. Epigenetics 5(6):509–515. doi:12224
208. Borah JC, Mujtaba S, Karakikes I, Zeng L, Muller M, Patel J, Moshkina N, Morohashi K, Zhang W, Gerona-Navarro G, Hajjar RJ, Zhou MM (2011) A small molecule binding to the coactivator CREB-binding protein blocks apoptosis in cardiomyocytes. Chem Biol 18(4):531–541. doi:10.1016/j.chembiol.2010.12.021
209. Hewings DS, Wang M, Philpott M, Fedorov O, Uttarkar S, Filippakopoulos P, Picaud S, Vuppusetty C, Marsden B, Knapp S, Conway SJ, Heightman TD (2011) 3,5-dimethylisoxazoles act as acetyl-lysine-mimetic bromodomain ligands. J Med Chem 54(19):6761–6770. doi:10.1021/jm200640v
210. Kung AL, Zabludoff SD, France DS, Freedman SJ, Tanner EA, Vieira A, Cornell-Kennon S, Lee J, Wang B, Wang J, Memmert K, Naegeli HU, Petersen F, Eck MJ, Bair KW, Wood AW, Livingston DM (2004) Small molecule blockade of transcriptional coactivation of the hypoxia-inducible factor pathway. Cancer Cell 6(1):33–43. doi:10.1016/j.ccr.2004.06.009
211. Block KM, Wang H, Szabo LZ, Polaske NW, Henchey LK, Dubey R, Kushal S, Laszlo CF, Makhoul J, Song Z, Meuillet EJ, Olenyuk BZ (2009) Direct inhibition of hypoxia-inducible transcription factor complex with designed dimeric epidithiodiketopiperazine. J Am Chem Soc 131(50):18078–18088. doi:10.1021/ja807601b
212. Best JL, Amezcua CA, Mayr B, Flechner L, Murawsky CM, Emerson B, Zor T, Gardner KH, Montminy M (2004) Identification of small-molecule antagonists that inhibit an activator: coactivator interaction. Proc Natl Acad Sci USA 101(51):17622–17627. doi:10.1073/pnas.0406374101
213. Li BX, Xiao X (2009) Discovery of a small-molecule inhibitor of the KIX-KID interaction. ChemBioChem 10(17):2721–2724. doi:10.1002/cbic.200900552
214. Buhrlage SJ, Bates CA, Rowe SP, Minter AR, Brennan BB, Majmudar CY, Wemmer DE, Al-Hashimi H, Mapp AK (2009) Amphipathic small molecules mimic the binding mode and function of endogenous transcription factors. ACS Chem Biol 4(5):335–344. doi:10.1021/cb900028j
215. Majmudar CY, Hojfeldt JW, Arevang CJ, Pomerantz WC, Gagnon JK, Schultz PJ, Cesa LC, Doss CH, Rowe SP, Vasquez V, Tamayo-Castillo G, Cierpicki T, Brooks CL 3rd, Sherman DH, Mapp AK (2012) Sekikaic Acid and Lobaric Acid Target a Dynamic Interface of the Coactivator CBP/p300. Angew Chem Int Ed Engl 51(45):11258–11262. doi:10.1002/anie.201206815
216. Yin S, Kaluz S, Devi NS, Jabbar AA, de Noronha RG, Mun J, Zhang Z, Boreddy PR, Wang W, Wang Z, Abbruscato T, Chen Z, Olson JJ, Zhang R, Goodman M, Nicolaou KC, Van Meir EG (2012) Arylsulfonamide KCN1 inhibits in vivo glioma growth and interferes with HIF signaling by disrupting HIF-1alpha interaction with co-factors p300/CBP. Clin Cancer Res. doi:10.1158/1078-0432.CCR-12-0861
217. Ward JJ, Sodhi JS, McGuffin LJ, Buxton BF, Jones DT (2004) Prediction and functional analysis of native disorder in proteins from the three kingdoms of life. J Mol Biol 337(3):635–645. doi:10.1016/j.jmb.2004.02.002