Cellular and Molecular Life Sciences

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

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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

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
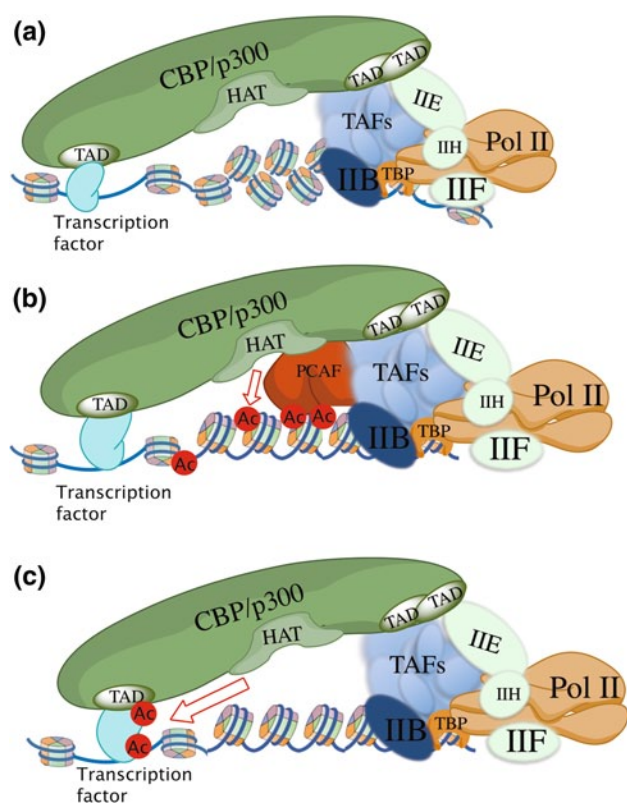

Fig. 1 Functional mechanisms of transcriptional activation by CBP/p300. CBP/p300 promotes transcriptional activity by recruiting transcriptional machinery to the promoter, and by modifying chromatin structure to facilitate transcription. **a** CBP/p300 functions as a "bridge", linking the DNA-bound transcription 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
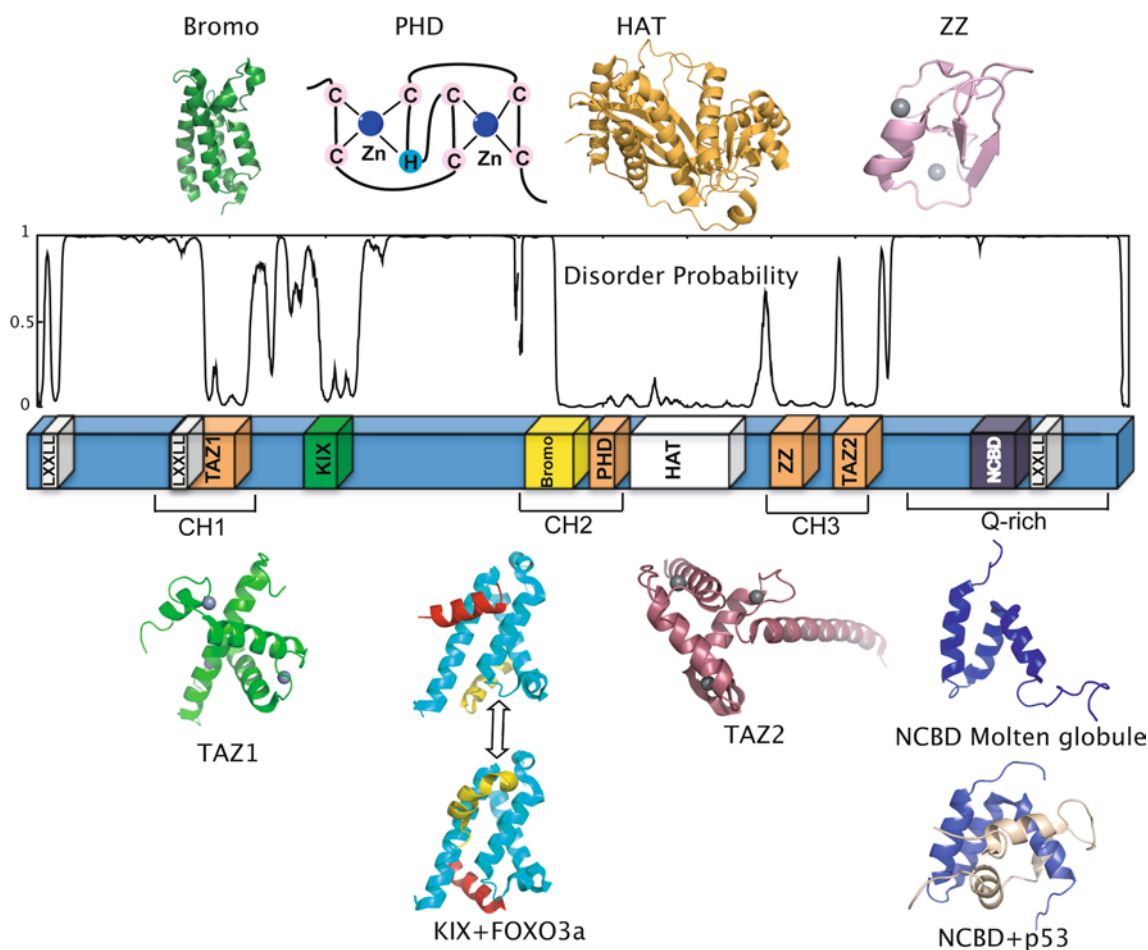
Fig. 2 Domain architecture and structures of domains of CBP/p300. The domain architecture of CBP/p300 is shown in the middle with the probability that regions are intrinsically disordered as predicted by DISOPRED2 [217]. The structures of each domain are also shown and labeled. *Top* the CBP Bromo domain (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 "$\phi XX\phi\phi$" motif, where ϕ is a hydrophobic residue, and X is an arbitrary residue. The "$\phi XX\phi\phi$" sequence forms an amphipathic helix placing the hydrophobic residues in the binding site groove. Interestingly, despite the conservation of the "$\phi XX\phi\phi$" motif, the exact mode of binding of "$\phi XX\phi\phi$" peptides is clearly not conserved. The "$\phi XX\phi\phi$" 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
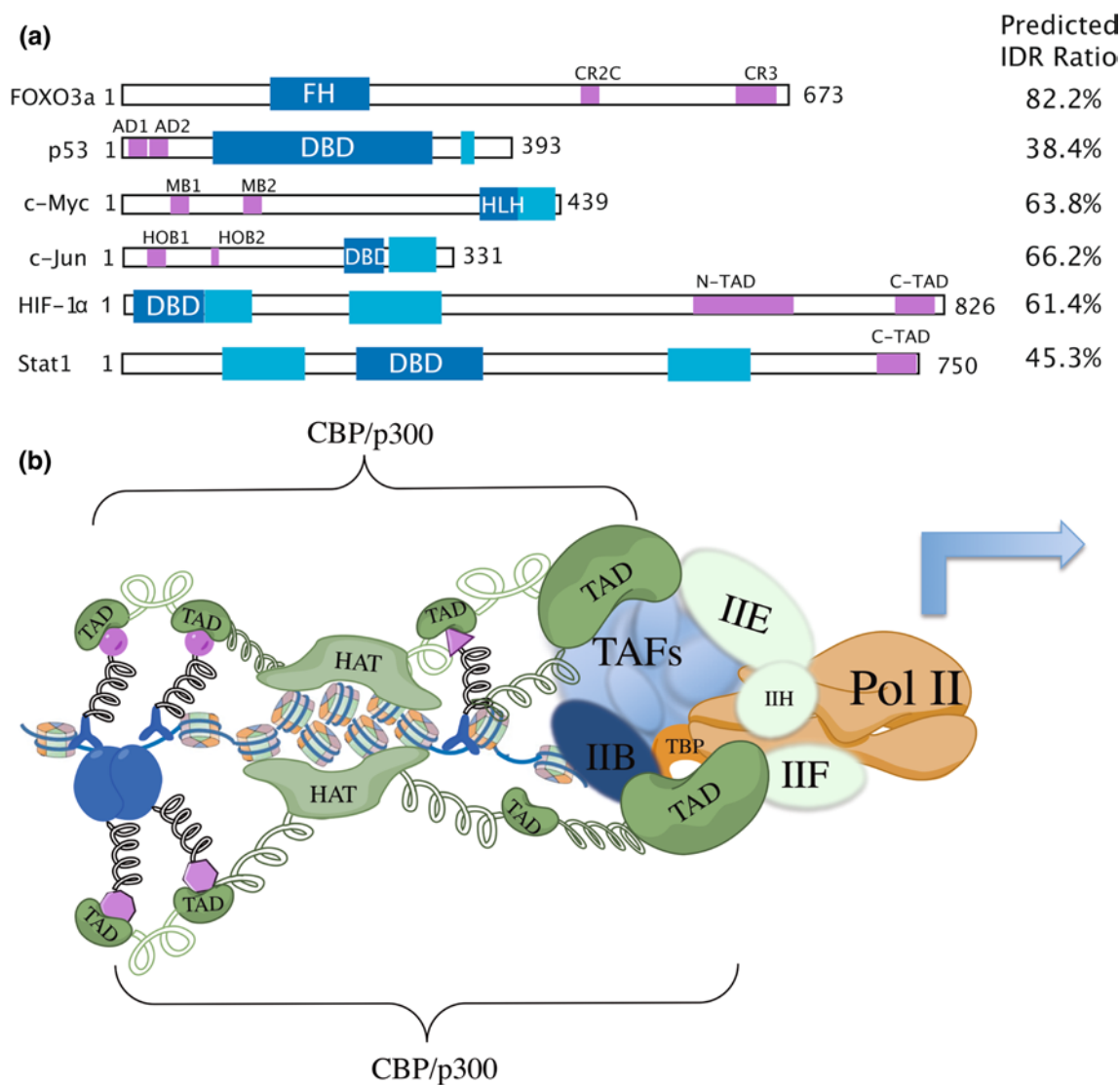
Fig. 3 Promiscuous multivalent model of CBP/p300 recruitment. **a** Many transcription factors contain tandem TADs located in intrinsically disordered regions (IDRs). DNA-binding domains are shown as *blue boxes*, other structured domains are indicated as *cyan boxes*, and TADs are labeled and colored *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
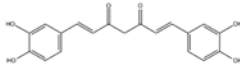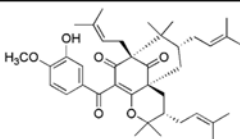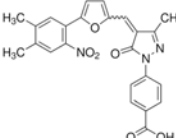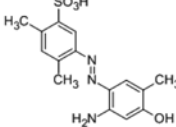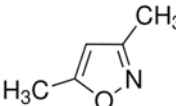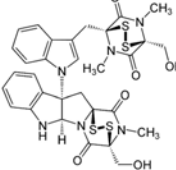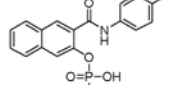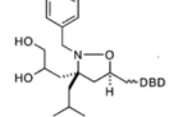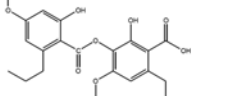
Name	Structure	Targeted domain	$IC_{50}/K_d(\mu M)$	Ref
Curcumin		HAT	$IC_{50}=25$	[200,201]
LTK-14		HAT	$IC_{50}=5-7$	[202,203]
C646		HAT	$IC_{50}=1.6$	[204]
Ischemin		Bromo	$IC_{50}=5$	[208]
3,5-dimethyl-isoxazole		Bromo	$IC_{50}=28$	[209]
Chetomin		TAZ1	$IC_{50}=1.5$	[211]
KG-501		KIX	$IC_{50}=2.9$	[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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