Front. Biol. 2018, 13(3): 168–179
https://doi.org/10.1007/s11515-018-1502-6

REVIEW

CBP/p300: intramolecular and intermolecular regulations

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BACKGROUND: CREB binding protein (CBP) and its close paralogue p300 are transcriptional coactivators with intrinsic acetyltransferase activity. Both CBP/p300 play critical roles in development and diseases. The enzymatic and biological functions of CBP/p300 are tightly regulated by themselves and by external factors. However, a comprehensive up-to-date review of the intramolecular and intermolecular regulations is lacking.
OBJECTIVE: To summarize the molecular mechanisms regulating CBP/p300s functions.
METHODS: A systematic literature search was conducted using the PubMed (https://www.ncbi.nlm.nih.gov/pubmed/) for literatures published during 1985-2018. Keywords "CBP regulation" or "p300 regulation" were used for the search.
RESULTS: The functions of CBP/p300, especially their acetyltransferase activity and chromatin association, are regulated both intramolecularly by their autoinhibitory loop (AIL), bromodomain, and PHD-RING region and intermolecularly by their interacting partners. The intramolecular mechanisms equip CBP/p300 with the capability of self-regulation while the intermolecular mechanisms allow them to respond to various cell signaling pathways.
CONCLUSION: Investigations into those regulation mechanisms are crucial to our understanding of CBP/p300s role in development and pathogenesis. Pharmacological interventions targeting these regulatory mechanisms have therapeutic potentials.

Keywords p300, CBP, histone acetylation, autoacetylation, HAT

Introduction

Transcription is critical to deciphering the commands encrypted in DNA to the completion of various biological processes. Regulation of this molecular event in eukaryotes is complex but strictly controlled, involving a network of numerous regulatory factors, such as cAMP response element binding protein (CREB) binding protein (CREBBP, aka CBP or lysine acetyltransferase 3A, KAT3A) and its close paralogue p300 (aka KAT3B) (Arany et al., 1994; Vo and Goodman, 2001). CBP and p300 were first identified as interacting proteins of CREB and adenoviral protein early region 1A (E1A), respectively (Chrivia et al., 1993; Eckner et al., 1994; Stein et al., 1990; Whyte et al., 1989; Yee and Branton, 1985). Both proteins contain intrinsic histone lysine acetyl-transferase (HAT, aka lysine acetyl-transferase or KAT) activity (Bannister and Kouzarides, 1996; Ogryzko et al., 1996) and constitute the KAT3 family in mammals.

Acetylation on histone lysine residues neutralizes the positive charge of the side chain, weakens the interaction between a histone and negatively charged DNA (Hong et al., 1993) and that between neighboring nucleosomes (Roth and Allis, 1996; Tessarz and Kouzarides, 2014). Moreover, histone acetylation also modulates chromatin at high-order structure levels (Tse et al., 1998). For instance, acetylation on histone H4K16 disturbs the formation of compact 30-nm chromatin fibers and prevents the generation of cross-fiber interactions by directly reducing the inter-nucleosome interaction (Shogren-Knaak et al., 2006; Zhang et al., 2017b). Consequently, an open chromatin structure is created

Received April 30, 2018; accepted June 1, 2018
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and the DNA is more accessible to the transcription machinery (Zhu and Li, 2016).

Histone acetylation also serves as a platform to recruit other factors to further remodel or modify the chromatin, which facilitates transcription (Kouzarides, 2007). Although in vitro CBP/p300 are able to acetylate multiple lysine residues of all four core histones (Ogryzko et al., 1996; Schiltz et al., 1999; Szerlong et al., 2010), *in vivo* they are mainly required for acetylation on K18 and K27 of histone H3 in nucleosomes (Horwitz et al., 2008; Jin et al., 2011). CBP/p300 can also acetylate H3K56 on free histones in response to DNA damage (Das et al., 2009; Vempati et al., 2010), which is required for chromatin reassembly after DNA repair (Chen et al., 2008). In addition to histones, CBP/p300 also acetylate numerous other proteins including many transcription factors (Dancy and Cole, 2015). In addition to their HAT activity, CBP/p300 also work as scaffolds to assemble mega transcriptional activation complexes; or serve as a bridge linking the activator complexes to the RNA polymerase II (Pol II) transcription machinery (Chan and La Thangue, 2001; Chen and Li, 2011; Kalkhoven, 2004). Consistent with their roles in transcriptional activation, CBP/p300 are mainly localized at regulatory DNA elements, especially enhancers (Heintzman et al., 2007; Wang et al., 2009). In fact, the genomic occupancy of CBP/p300 has been used as a predictive marker for active enhancers (Visel et al., 2009).

Considering the many roles of CBP/p300 in transcription control, it is not surprising that they are essential to various physiologic processes such as cell proliferation, differentiation and development (Goodman and Smolik, 2000). Mice homozygous null for either CBP (*Crebbp*$^{-/-}$) or p300 (*Ep300*$^{-/-}$) are embryonic lethal (Oike et al., 1999; Tanaka et al., 2000; Yao et al., 1998). *Crebbp*$^{-/-}$ mice died around embryonic day 10.5~12.5 (E10.5~E12.5) (Tanaka et al., 2000) while *Ep300*$^{-/-}$ died around E9.0~E11.5 (Yao et al., 1998). Both mutant embryos displayed severe defect in growth and neural tube closure (Yao et al., 1998). In addition, double heterozygotes *Crebbp*$^{+/-}$*Ep300*$^{+/-}$ are embryonic lethal and single heterozygotes also showed reduced viability and multiple defects (Kung et al., 2000; Tanaka et al., 1997; Yao et al., 1998). These studies suggest that CBP and p300 exert some overlapping functions in embryonic development in a dosage-dependent manner. However, it has also been reported that CBP/p300 play distinct roles. For example, although both CBP (Kung et al., 2000) and p300 (Kasper et al., 2002) are crucial for hematopoiesis, they seem to play distinct roles in this process. CBP, but not p300, is critical to hematopoietic stem cell self-renewal while p300 plays more important roles in hematopoietic differentiation (Rebel et al., 2002). In addition, CBP and p300 function differently in retinoic-acid (RA)-induced cell differentiation and cell cycle regulation (Kawasaki et al., 1998), and other processes (Kalkhoven, 2004; Kasper et al., 2006).

Dysregulation of CBP/p300 has been implicated in many types of human diseases. For example, heterozygous mutations/deletions of *CREBBP* or, less commonly, *EP300*, cause Rubinstein–Taybi syndrome (RTS), a rare human genetic disorder characterized by mental retardation and physical abnormalities (Petrij et al., 1995;Solomon et al., 2015). *CREBBP* and *EP300* are among the most frequently mutated genes in human cancers. CBP/p300 has been reported to play a role in promoting oncogenesis of certain types of cancers including prostate cancer (Debes et al., 2003; Zhong et al., 2014) and acute myeloid leukemia (AML) (Giotopoulos et al., 2016; Roe et al., 2015), whereas they can also work as tumor suppressors in other types of cancers such as B cell lymphoma (Horton et al., 2017; Jiang et al., 2017;Zhang et al., 2017a).

Although the mechanisms underlying CBP/p300-mediated transcriptional regulation have been well documented, a comprehensive summary of how CBP/p300 themselves are regulated is lacking. In this review, we describe how the protein domains/ functional regions within CBP/p300 modulate their acetyltransferase activity and chromatin association, followed by an outline of external factors that contribute to CBP/p300 regulation and their clinical relevance.

Intramolecular regulations of CBP/p300

CBP and p300 proteins are composed of multiple conserved protein domains. These include (from N- to C terminus) a nuclear receptor-interacting domain (NRID), a transcriptional adapter zinc binding (TAZ1) domain, a kinase-inducible domain interacting (KIX) domain, a bromodomain (BRD), a combined Really Interesting New Gene (RING) domain and plant homeodomain (PHD), a HAT domain, a ZZ-type zinc finger (ZZ), another TAZ domain (TAZ2) and an interferon binding domain (IBiD) (Fig. 1A) (Dancy and Cole, 2015). Of note, the TAZ1, RING-PHD and ZZ-TAZ2 domains each contains a cysteine/histidine-rich region (CH), namely CH1, CH2 and CH3, respectively. The HAT domain and its adjacent BRD, CH2 and CH3 form the catalytic core of CBP/p300 (Park et al., 2017). Other domains and regions are linked to the catalytic core by long stretches of unstructured regions. These domains and regions not only directly regulate the co-activator function of CBP/p300, but also serve as platforms for other external interacting factors to regulate CBP/p300.

Regulation of CBP/p300 by the autoinhibitory loop (AIL)

The autoinhibitory loop (AIL, aka autoregulatory loop or activation loop) is a lysine-rich loop region adopting a disordered structure within the HAT domain (Delvecchio et al., 2013; Park et al., 2017). It is composed of amino acid (aa) residues 1520-1581 of p300 and aa 1556-1618 of CBP in humans. AIL was discovered by the Philip Cole laboratory during their study of autoacetylation in the regulation of

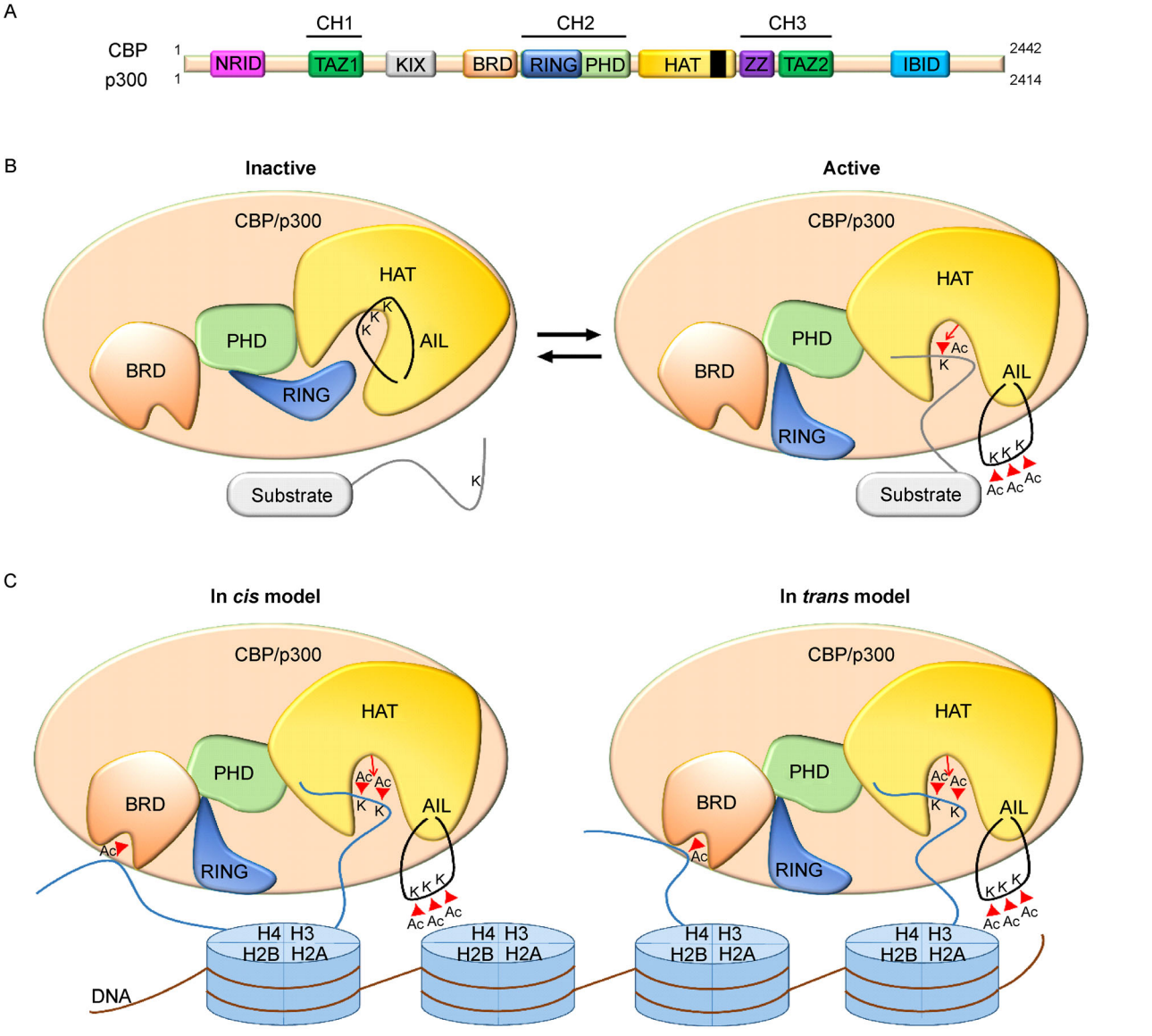

Figure 1 Regulation of CBP/p300 acetyltransferase activity by AIL, RING domain and BRD. (A) Schematic representation of human CBP/p300 domain architecture. The numbers of residues are also labeled. (B) The HAT domain is in inactive state because hypoacetylated AIL occupies the substrate binding groove and also because RING domain is packed in close proximity to the HAT active site. CBP/p300 AIL can be autoacetylated *in trans*. HAT domain will become activated when RING domain and the hyperacetylated AIL are displaced from the catalytic site. (C) CBP/p300 BRD is a reader domain preferentially binds acetylated histone H4. The recognition of acetylated histone tail by BRD not only directly recruits CBP/p300 to chromatin but also increases the accessibility of histone substrate, for example, H3, to HAT domain, thus enhancing histone acetylation. Both in *cis* and in *trans* models are shown.

p300s HAT activity (Thompson et al., 2004). Up to 17 lysine residues in the AIL and nearby regions of p300 can be autoacetylated through an intermolecular mechanism (Karanam et al., 2006). When AIL is hypoacetylated, it occupies the HAT domain active site and inhibits the acetyltransferase activity by competing with positively-charged substrates such as histone tails (Liu et al., 2008). Once hyperacetylated, AIL is displaced from the catalytic site leaving the active site exposed to substrates (Fig. 1B). Deletion of AIL can release the active site as does AIL hyperacetylation, creating a constitutively active HAT (Thompson et al., 2004). Surprisingly, a recent study showed that deletion of AIL in CBP specifically impairs acetylation of p53 proteins on K382 but not acetylation of histones (Park et al., 2017), implying the existence of more complicated mechanisms in AIL-mediated CBP/p300 regulation.

Compared with the HAT domain of other proteins such as GCN5/PCAF, p300 HAT has a more promiscuous substrate

specificity, which can be explained by its two unique features. First, the substrate-recognition pocket of p300 HAT domain is shallower and more negatively-charged than other HATs (Liu et al., 2008; Trievel et al., 1999). Second, p300 HAT utilizes a Theorell – Chance (also called "hit-and-run") catalytic mechanism (Thompson et al., 2001) so that it does not require a specific substrate binding pocket, whereas GCN5/PCAF employs the classic Bi-Bi ternary complex mechanism (Rojas et al., 1999). It is possible that other regions or factors may also affect the substrate specificity of HAT domain by altering the conformation of the substrate binding groove.

In addition to the modulation of HAT activity, AIL also plays a role in regulating CBP/p300 chromatin association. In an in vitro system, autoacetylation of AIL induces the dissociation of p300 from the preinitiation complex (PIC) containing GAL4-VP14 and Mediator, which enhances TFIID binding and transcription initiation (Black et al., 2006). Autoacetylation is thought to induce conformational change of CBP/p300 HAT domain (Black et al., 2006) but the structural basis of this change is still elusive.

Regulation of CBP/p300 by the RING-PHD region

The cysteine/histidine-rich CH2 between the BRD and HAT domains is comprised of a RING domain and a PHD-type zinc finger and plays an important role in modulating the catalytic activity of CBP/p300. Crystal structure of the p300 catalytic core encompassing the BRD, CH2 and HAT domains reveals that the PHD-type zinc finger is discontinuous due to the interruption by the RING domain (Delvecchio et al., 2013). The BRD-RING-PHD-HAT segment forms a compact structural module with RING-PHD serving as a bridge to connect BRD and HAT by interacting with both domains. The RING domain is packed in close proximity to the HAT domain and contacts the substrate binding loop of HAT. Deletion or mutations of RING impairing structural integrity or its interaction with HAT enhances p300 autoacetylation (on K1499) and acetylation of the p53 substrate (on K382) (Delvecchio et al., 2013; Rack et al., 2014), suggesting a negative role of RING in regulating the HAT domain of p300. The RING domain of CBP shows a similar regulatory role in CBP autoacetylation and p53K382 acetylation (Park et al., 2017).

In contrast to p53 acetylation, RING deletion in p300 reduces acetylation on histone H3K9 and H3K14 (Rack et al., 2014), whereas in the case of CBP, RING deletion has no dramatic effect on histone acetylation (Park et al., 2017). These results suggest that the regulatory role of RING in CBP/p300 acetyltransferase activity may be substrate-specific. It is intriguing to know how the RING domain differently regulates HAT domain in acetylating distinct substrates.

In contrast to the RING mutations, mutations in PHD or in PHD-HAT interfaces have little effect on p300 autoacetylation or p53 acetylation (Delvecchio et al., 2013). In addition, the PHD domain is likely not directly involved in regulation of p300/CBP chromatin binding. Unlike the canonical PHD domains that function as readers of modified or unmodified histones (Sanchez and Zhou, 2011; Shi et al., 2006), the CBP/p300 PHD does not recognize histones due to the lack of conserved residues critical for histone binding (Delvecchio et al., 2013; Park et al., 2013). The actual function of the PHD-type zinc finger in CBP/p300 still remains unknown.

Regulation of CBP/p300 by BRD

Acetylated histone lysines are recognized by specific reader proteins, which facilitates the recruitment or retention of transcription co-activators at acetylated chromatin loci. BRD is the first discovered reader of histone acetylation and has been extensively studied since the initial discovery (Dhalluin et al., 1999). The BRDs in CBP/p300 exhibit histone- and nucleosome binding capability (Manning et al., 2001; Ragvin et al., 2004). They bind to many acetylated histone peptides in vitro, preferentially di- and tri-acetylated histone H4 and H2B (Delvecchio et al., 2013; Park et al., 2013). This preference is further supported by nuclear magnetic resonance (NMR) studies (Zeng et al., 2008) and crystal structures (Plotnikov et al., 2014). Recently, it has been reported that CBP BRD can also bind with high affinity to H3K56ac, a product catalyzed by CBP/p300 on free histones (Das et al., 2014; Xu et al., 2017). Similar to many other BRDs, a conserved asparagine within the hydrophobic acetyllysine binding pocket is critical to the ability of p300/CBP binding to acetylated histones. Substitution of Asn1132 (N1132) of p300 BRD to alanine abolishes its binding to all acetylated histone peptides (Delvecchio et al., 2013).

Although the CBP/p300 BRDs are not adjacent to the HAT domains, they are crucial to CBP/p300-mediated histone acetylation. Deletion of BRD greatly impairs the ability of p300 to acetylate histones in nucleosome (Nguyen et al., 2014), native chromatin (Kraus et al., 1999) and recombinant chromatin (Tang et al., 2013) in vitro. In cells, the increase in global H3K9ac and H3K14ac levels caused by ectopic p300 overexpression is abolished by BRD deletion or mutations in its acetyllysine binding pocket (Rack et al., 2014). Interestingly, in contrast to its critical role in histone substrate acetylation, loss of BRD does not significantly affect p300 autoacetylation and the acetylation of non-histone substrate such as p53, indicating that BRD is not required for p300 intrinsic acetyltransferase activity (Delvecchio et al., 2013; Kraus et al., 1999; Tang et al., 2013). Considering its nature as a histone acetylation reader, BRD may function as a "hand" that grabs acetylated histone tails, thus increasing the accessibility of nucleosome substrates to the catalytic HAT

domain of CBP/p300 (Fig. 1C). This model is supported by a recent finding that preexisting H4 acetylation enhances p300 HAT activity on H3K18ac, while this enhancement is not observed in p300 with BRD deletion or mutations (Nguyen et al., 2014). However, currently it is not clear whether the recognition of acetylated H4 by BRD facilitates acetylation of the H3 within the same nucleosome as this BRD-bound H4 (in *cis* model) or in the adjacent nucleosome (in *trans* model) (Fig. 1C). Deletion of BRD also prevents p300 from forming stable and direct interaction with nucleosomes (Manning et al., 2001); and treatment of CBP30, a small-molecule inhibitor targeting CBP/p300 BRD, displaces CBP/p300 from chromatin in cells (Ghosh et al., 2016; Hammitzsch et al., 2015), suggesting that a functional BRD is required for CBP/p300-chromatin association.

The abovementioned essential role of CBP/p300 BRD in chromatin binding and histone acetylation explains the requirement of BRD in CBP/p300-mediated gene activation (Fonte et al., 2005) and transcription enhancement (Kraus et al., 1999). Consistently, CBP30 treatment dramatically reduces H3K18ac and H3K27ac levels at multiple CBP/p300 target loci along with deactivation of target gene transcription in cells (Conery et al., 2016; Ghosh et al., 2016). All together, these data suggest that the cooperation between BRD and HAT ensures efficient transcription activation by p300/CBP.

Although deletion of BRD does not affect CBP/p300 AIL autoacetylation (Delvecchio et al., 2013; Kraus et al., 1999; Tang et al., 2013), autoacetylation of CBP AIL (at K1596) negatively regulates its BRD's function. The acetylated K1596 is recognized by BRD, thus preventing BRD from binding to acetylated histones, reducing CBP-chromatin association (Park et al., 2017). This discovery provides a possible explanation for the autoacetylation-induced dissociation of CBP/p300 from chromatin, which allows PIC to form at the same chromatin loci to initiate transcription (Black et al., 2006). In addition, binding of K1596ac to BRD also attenuates the function of CBP BRD in enhancing histone acetylation (Park et al., 2017). These results suggest that CBP/p300 autoacetylation is not always associated with increased HAT activity.

Intermolecular regulations of CBP/p300

In addition to the intramolecular regulations, CBP/p300 are also subjected to regulation by numerous external molecules. The intermolecular regulations are critical to CBP/p300s functions in response to various cell signaling pathways (Chakravarti et al., 1996; Goodman and Smolik, 2000). Upon the perception of intra- or extracellular signals, cells initiate a series of molecular events of signal transduction, leading to activation of a group of genes and deactivation of others. CBP/p300 plays indispensable roles in activating gene expression in responses to almost all signaling pathways. CBP/p300 receive and execute commands from upstream signals through signal-induced protein–protein interactions and post-translational modifications (PTMs), which modulate the dynamics of chromatin association and HAT activity of CBP/p300.

Regulation of CBP/p300 by protein–protein interactions

Till date, more than 400 proteins have been reported to interact with CBP/p300 (Dancy and Cole, 2015), including transcription factors, coactivators, mediators and basal transcription machinery components. These protein–protein interactions allow CBP/p300 to integrate the assembly of transcription activation complexes, connect them to basal transcription machinery, and get access to some of these proteins for substrate acetylation (Dancy and Cole, 2015; Wang et al., 2013a).

CBP/p300 contain a number of small structured domains that are used to interact with binding partners, more often with NRID, TAZ1, KIX, TAZ2, IBiD motifs, and to a less extent, BRD and HAT domains (Wang et al., 2013a). These domains often function as scaffolds to accommodate the intrinsically disordered or partially disordered regions of their binding partners (Dyson and Wright, 2016). Recently, the disordered linker regions of CBP/p300 that are between the structured domains have also been reported to mediate interactions with other proteins (Contreras-Martos et al., 2017). Notably, one protein may interact with multiple domains or regions of CBP/p300 simultaneously.

The proteins interact with CBP/p300 are important for CBP/p300 to associate with chromatin. As CBP/p300 do not contain specific DNA binding domains, recruitment of CBP/p300 to specific genomic loci, such as enhancers or gene promoters, is achieved by interacting with transcriptional factors that bind to specific DNA sequences. A well-studied example is CREB, a transcription factor that recognizes the DNA sequence known as cAMP-response elements (CREs). Accumulation of cAMP upon activation of G protein-coupled receptors (GPCRs) promotes the catalytic subunit of protein kinase A (PKA) to dissociate from the regulatory domain, diffuse into nucleus, and phosphorylate the kinase-inducible domain (KID) of CREB (Mayr and Montminy, 2001). KID phosphorylation (at Serine 133) greatly increases its binding to the KIX domain of CBP, thus the CREB-CBP interaction recruits CBP to CREs, leading to activation of cAMP-responsive genes (Chrivia et al., 1993; Kwok et al., 1994). The hydrogen bond formed between phosphorylated Ser133 of CREB and Tyr658 of CBP KIX domain plays an indispensable role in the KID-KIX interaction (Radhakrishnan et al., 1997). Upon interaction with KIX, the unstructured KID undergoes a coil-to-helix transition, forming two helices, with one of the helices interacting with the hydrophobic

groove of KIX, stabilizing the direct contact between KID and KIX (Radhakrishnan et al., 1997).

Intermolecular protein–protein interactions also directly regulate the HAT activity of CBP/p300. P300 is originally discovered as one of the proteins that bind E1A, an adenoviral oncoprotein (Whyte et al., 1989; Yee and Branton, 1985). Small E1A protein (e1a) contains three conserved regions (CR), with CR1 and CR2 interacting with CBP/p300 and retinoblastoma (RB) proteins, respectively (Berk, 2005). Binding of e1a to the TAZ2 domain inhibits the HAT activity of CBP/p300 toward histones in vitro, thus repressing CBP/p300-dependent transcription (Chakravarti et al., 1999; Hamamori et al., 1999; Perissi et al., 1999). Infection of cells with adenovirus Type 5 (Ad5) *dl1500* that expresses only e1a markedly reduces global H3K18 acetylation level, which mimics the depletion of both CBP and p300 (Horwitz et al., 2008). Interestingly, e1a can be acetylated at K239 by CBP/p300, implying that as a substrate of CBP/p300, e1a may inhibit the HAT activity by directly competing with histones for the catalytic site of CBP/p300 (Madison et al., 2002).

In contrast to e1a that inhibits CBP/p300 HAT activity, Mastermind like 1 (MAML1) binds to the TAZ2 domain of p300 to promote its HAT activity both in vitro (Saint Just Ribeiro et al., 2007) and in vivo (Hansson et al., 2009), probably through potentiating p300 autoacetylation (Hansson et al., 2009). MAML1 also helps to recruit p300 to the genomic loci of Notch pathway genes (Fryer et al., 2002), suggesting that MAML1 regulates both the HAT activity and chromatin association of p300.

Regulation of CBP/p300 by RNA interaction

In addition to protein interactors, a recent exciting study revealed that CBP also directly binds to RNAs (Bose et al., 2017). CBP-bound RNAs mostly arise from the chromatin regions with high occupancy of CBP and a large fraction of them are enhancer RNAs (eRNAs). Enhancer RNAs are non-coding RNAs transcribed by the DNA sequences of enhancers (Kim et al., 2010). Those eRNAs directly bind to CBP AIL and displace it from the HAT active site, thus stimulating the HAT activity of CBP in vitro. Consistently, depletion of a certain eRNA in cells greatly reduces histone acetylation levels (on H3K18 and H3K27) on the same enhancer and its associate promoter without affecting CBP occupancy (Bose et al., 2017). This study suggests that when CBP is recruited to active enhancers where eRNAs were produced and locally enriched, eRNAs can bind to the AIL of CBP to stimulate its HAT activity, leading to a local increase of CBP-dependent histone acetylation at the same enhancer and associated promoters. This finding also indicates that in addition to AIL autoacetylation, cells may employ multiple mechanisms to ensure AIL is displaced from the HAT active site, safeguarding histone acetylation and gene activation.

Regulation of CBP/p300 by post-translational modifications (PTMs)

While CBP/p300 catalyze lysine acetylation on histones and other proteins, they themselves are also subject to PTMs, such as phosphorylation, methylation and SUMOylation, that in turn affects the functionality and homeostasis of CBP/p300. CBP/p300 can be phosphorylated at various sites. For example, AKT phosphorylates p300 at S1834 (Huang and Chen, 2005), ERK1/2 phosphorylates p300 at three serine residues (S2279, S2315 and S2366) (Chen et al., 2007), and mTORC1 phosphorylates p300 at four serine residues (S2271, S2279, S2291 and S2315) (Wan et al., 2017). All these phosphorylation events stimulate HAT activity, whereas in contrast, PKC-catalyzed p300 phosphorylation at S89 inhibits the catalytic activity of p300 (Yuan et al., 2002). It has remained elusive for a long time how phosphorylation at the distal N- or C-terminal regions of p300 modulates HAT domain that is located in the center region. A recent study by Wan et al. reveals that mTORC-catalyzed p300 phosphorylation abrogates the interaction between the HAT and RING domains, thus releasing the HAT catalytic site from the inhibitory RING (Wan et al., 2017). This finding indicates the existence of crosstalk between inter- and intramolecular regulation mechanisms of CBP/p300.

Phosphorylation also regulates CBP/p300 homeostasis. For instance, p300 S106 phosphorylation by ATM promotes p300 protein stabilization in response to double-strand breaks (DSBs) (Jang et al., 2010), while MAPK/AKT-dependent p300 S1834 phosphorylation induces p300 degradation in nucleotide excision repair (NER) pathway (Wang et al., 2013b).

In addition to phosphorylation, other PTMs also contribute to CBP/p300 regulation. Coactivator-associated arginine methyltransferase 1 (CARM1) interacts and methylates CBP/p300 at multiple arginine residues (Chevillard-Briet et al., 2002; Lee et al., 2005; Xu et al., 2001). Methylation of arginine at different regions has distinct regulatory roles on CBP/p300. For example, methylation within the KIX domain disrupts its interaction with CREB and reduces chromatin recruitment of CBP/p300 (Xu et al., 2001); while methylation of arginine located downstream of KIX increases the recruitment of CBP to estrogen receptor (ER) -responsive target genes and enhances CBP HAT activity (Ceschin et al., 2011; Chevillard-Briet et al., 2002). In addition, SUMOylation of CBP/p300 on the lysines upstream of BRD negatively regulates CBP/p300-mediated transcription, and such repression appears to involve recruitment of histone deacetylases (HDAC) (Girdwood et al., 2003; Kuo et al., 2005).

Clinical relevance

Investigations into the regulation mechanisms not only facilitate our understanding of molecular and biological

functions of CBP/p300, but also have important clinical relevance. Genes encoding CBP and p300 are frequently mutated in genetic disorders and human cancers (Korzus, 2017; Martincorena and Campbell, 2015). Most genetic mutations are located within the HAT domains, some of which have been reported to affect acetyltransferase activity (Morin et al., 2011; Mullighan et al., 2011; Pasqualucci et al., 2011; Peifer et al., 2012). In addition, large numbers of recurrent mutations are also found in other regulatory domains. For example, CBP RING domain mutations C1240R and E1278K were found in B cell lymphoma and RTS, respectively. Both mutations enhance CBP autoacetylation and the acetylation of non-histone substrate p53, probably through abrogating the interaction between RING and HAT domains (Delvecchio et al., 2013; Rack et al., 2014). Together, these cases suggest that abnormalities in CBP/p300 regulation contribute to pathogenesis.

Extensive efforts have been made to identify small molecules targeting CBP/p300 HAT domain. For example, Lys-CoA, the first synthesized inhibitor for CBP/p300 HAT (Lau et al., 2000), has been used in structural (Liu et al., 2008) and enzymatic (Thompson et al., 2001) studies as well as drug discovery (Bowers et al., 2010) for many years. Recently, C646 (Bowers et al., 2010) and A-485 (Lasko et al., 2017; Michaelides et al., 2018) compounds were developed with increased specificity and potency toward CBP/p300 HAT domain. Inhibitors targeting regulatory regions have also been developed. For example, chetomin and epidithiodiketopiperazine (ETP) can disrupt the interaction between p300/CBP TAZ1 domain and transcription factor HIF-1α, thus inhibiting hypoxia-inducible genes expression and cancer cell growth (Block et al., 2009; Kung et al., 2004). Small molecule KG-501 binds the KIX domain CBP/p300 and block its interaction with CREB and other proteins (Best et al., 2004). Furthermore, inhibitors targeting the BRD of CBP/p300, including CBP30 and I-CBP112, are able to abrogate the binding of BRD to acetylated histones, modulate HAT activity and displace CBP/p300 from chromatin (Ghosh et al., 2016; Hammitzsch et al., 2015; Picaud et al., 2015; Zucconi et al., 2016). These compounds have shown promising results in several pre-clinic trials in modulating T cells (Ghosh et al., 2016; Hammitzsch et al., 2015), and treating AML (Picaud et al., 2015) and multiple myeloma (Conery et al., 2016). Although there is still a long way to go for these small molecule inhibitors from bench to bedside, understanding the regulatory mechanisms of CBP/p300 in basic research settings is the indispensable first step toward future applications at clinic.

Conclusion remarks

Since the first discovery of p300/CBP more than 30 years ago, numerous research articles have been published to address the biochemical and molecular characteristics of those two proteins and their biological significance in development, metabolism and human diseases. These studies help to reveal multiple non-exclusive regulatory mechanisms, involving their own protein domains and interacting partners (Fig. 2). The intramolecular mechanisms provide CBP/p300 intrinsic capability for self-regulation, whereas the intermolecular mechanisms allow for quick responses to various cellular signaling pathways. Intra- and intermolecular regulation mechanisms are not mutually exclusive; frequent crosstalk between them is believed to play a critical role in physiologic

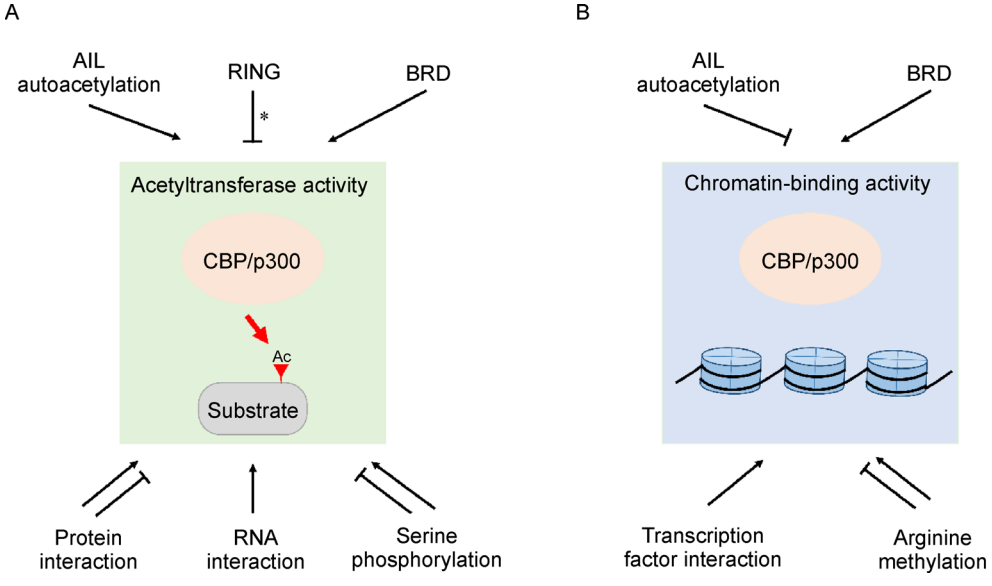

Figure 2 Summary of intramolecular and intermolecular mechanisms regulating CBP/p300 acetyltransferase activity (A) and chromatin association (B). Lines with arrows indicate positive regulation whereas blunt-ended lines indicate negative regulation. *: the negative regulatory role of RING domain in CBP/p300 acetyltransferase activity is specific to non-histone substrate.

and disease settings. It is thus urgent to understand of how the regulatory regions coordinate with each other not only in the context of the CBP/p300 proteins but also in large protein complexes. Structural biology methodologies such as Cryo-EM will be beneficial in this aspect. Knowledges gained from these studies will also provide basis for improvement of small molecules targeting regulatory domains for future pharmacological interventions in cancer therapy.

Compliance with ethics guidelines

The authors declare no conflict of interest. This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

Acknowledgments

We thank members of the Shi laboratory for discussions. This work was supported in part by grants from NIH/NCI (CA204020) and Leukemia & Lymphoma Society (1339-17) to X.S.. X.S. is a Scientific Advisory Board member of EpiCypher.

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