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Genomic occupancy of the transcriptional co-activators p300 and CBP

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The p300 and CBP co-activators are histone acetylases and central regulators of transcription in metazoans. The genomic occupancy of p300/CBP detected by ChIP-seq experiments can be used to identify transcriptional enhancers. However, studies in Drosophila embryos suggest that there is a preference for some transcription factors in directing p300/CBP to the genome. Although p300/CBP occupancy in general correlates with gene activation, they can also be found at silent genomic regions, which does not result in histone acetylation. Polycomb-mediated H3K27me3 is associated with repression, but does not preclude p300/CBP binding. An antagonism between H3K27ac and H3K27me3 indicates that p300/CBP may be involved in switching between repressed and active chromatin states.

Keywords: transcription, p300, CBP, ChIP-seq, enhancer, Polycomb

Abbreviations: CBP, cyclic-AMP response element binding protein (CREB)-binding protein; ChIP, Chromatin immunoprecipitation; HAT, histone acetyltransferase; H3K27ac, Histone 3 lysine 27 acetylation; H3K27me3, Histone 3 lysine 27 tri-methylation; p300, adenovirus early region 1A (E1A)-interacting protein of 300 kDa; HOT region, high occupancy target region

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Introduction

CREB-binding protein (CBP) and its paralog p300 are central regulators of gene expression in metazoan cells. They were originally identified as binding partners of the cAMP-response element binding (CREB) protein,[1] and the adenovirus early-region 1A (E1A) protein.[2,3] Today, over 400 interaction partners have been described for these proteins,[4] including transcription factors of all major families. They can function as transcriptional adaptors between enhancer-bound transcription factors and the basal transcription machinery. They also contain an intrinsic histone acetyltransferase (HAT) activity, and have been reported to acetylate over 70 other proteins, including themselves.[5] In vitro, p300/CBP are promiscuous acetyltransferases that can acetylate histones and non-histone proteins at many residues. However, histone 3 lysine 18 (H3K18) and H3K27 are major in vivo targets.[6,7] In addition, H3K56 can be acetylated by p300/CBP in response to DNA damage.[8]

As well as the enzymatic HAT domain, p300 and CBP contain three cysteine-histidine-rich domains (CH1, CH2 and CH3), a KIX-domain, a steroid receptor co-activator interaction domain (SID) and a bromodomain. These serve as protein-protein interaction domains, where the bromodomain recognizes acetyl-lysine in histones and other proteins.[9] The mechanisms by which these co-activators facilitate gene activation by transcription factors are not entirely understood. It may involve the adaptor function to bridge transcription factors with basal factors, leading to recruitment of RNA polymerase II, a scaffolding function to facilitate protein-protein and protein-DNA interactions, or involve their intrinsic acetyltransferase activity (**Fig. 1B**). Most likely, the activity of p300/CBP that is most important for transcription activation is going to vary from gene to gene and/or cellular conditions, or may function together as a means to accommodate multiple transcriptional inputs into a network of activation.

Loss of p300 or CBP gene function disrupts development and is lethal in mice, worms and flies.[10] CBP and p300 are targets of DNA tumor virus transforming proteins, and binding to these viral proteins causes a dramatic redistribution of H3K18ac across the host genome.[11,12] Dysregulation of p300/CBP results in human disease. For example, CBP or p300 heterozygosity causes Rubinstein-Taybi Syndrome,[13] and CBP as well as p300 are disrupted by chromosomal translocations with MLL or other partners in certain

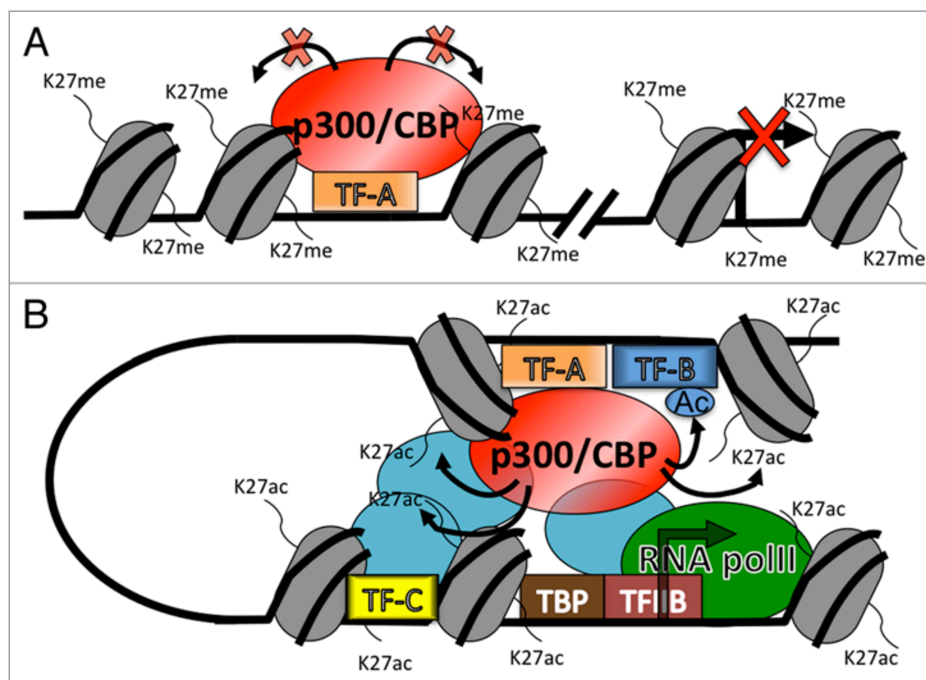

Figure 1. (A) Genes that are silenced by Polycomb-mediated H3K27me3 (K27me) can be occupied by p300/CBP. Association of p300/CBP with silent or poised transcriptional enhancers (with or without H3K27me3) does not result in histone acetylation. (B) At active genes, p300/CBP can acetylate histones on H3K27 (K27ac) and H3K18 (not shown), acetylate transcription factors (Ac), function as scaffolds for recruiting other proteins, or help establish a preinitiation complex by interactions with TFIIB and hypophosphorylated RNA polymerase II.

leukemia.[14] Recent exome sequencing efforts have revealed frequent inactivating mutations in CBP and p300 in B-cell lymphoma and in relapsed acute lymphoblastic leukemia.[15,16] Therefore, understanding how p300/CBP occupies the genome and regulates gene transcription is of wide interest for deciphering general mechanisms of transcriptional control, as well as for insights into the etiology of some human disease.

Genome Occupancy of p300/CBP Predicts Enhancer Sequences

Since p300/CBP are among the most widely used transcriptional co-activators in metazoans, they are expected to occupy the genome at many cis-regulatory DNA sequences together with numerous different transcription factors. Chromatin immunoprecipitation (ChIP) of p300/CBP followed by massively parallel sequencing (ChIP-seq) has confirmed this prediction, and has shown that most p300/CBP peaks are located at DNase I hypersensitive sites in both promoters and in intergenic regions.[17] A few genomic regions are occupied by either p300 or CBP, but a vast majority of the regions are occupied by both p300 and CBP, suggesting that they have largely overlapping functions.[17,18] A landmark paper from the Ren laboratory showed that gene-distal p300 binding regions overlap with histone H3K4 monomethylation, and that these peaks are signatures of transcriptional enhancers.[19] ChIP-seq of p300/CBP was later shown to successfully predict novel tissue-specific enhancers.[20,21] In fact, determining genome occupancy of p300/CBP and histone H3K4me1 by ChIP-seq is currently the most successful strategy to identify novel transcriptional regulatory sequences.[22]

However, what fraction of regulatory sequences that can be identified through genome occupancy of p300/CBP is not known. Heintzman et al.[19] reported that about one quarter of 389 predicted enhancers overlap p300 ChIP-chip binding sites. One reason for not observing stronger overlap could be that p300/CBP is bound at levels below the criteria used for defining peaks. We found that CBP binding to many known enhancer sequences that are active in early Drosophila embryos is below the cut-off we used for high-confidence peaks.[23] Nevertheless, average CBP occupancy was 1.73 times the genomic background at 97 previously described early embryonic enhancers. This indicates that p300/CBP may be occupying many enhancers at low levels. We also found that CBP binding differs greatly between wild-type and mutant embryos, and that some gene regulatory networks rely on CBP to a much larger extent than others. This is consistent with the finding that p300/CBP ChIP-seq from different tissues defines enhancers that are active in a tissue-specific manner.[21] Therefore, mapping p300/CBP binding in different cell-types will increase the number of putative regulatory sequences that can be predicted. Still, a substantial number of enhancers will probably require alternative strategies for their identification, e.g., genome occupancy of other HATs[24] or co-activators.[19]

What Recruits p300/CBP to the Genome?

The cellular levels of p300/CBP are limiting,[10,25] suggesting that only a subset of all genes are targeted by these proteins, and

that the gene targets change under different conditions. Although p300/CBP interacts with many transcription factors of different kind, whether some factors are more important than others in recruiting p300/CBP to regulatory DNA in vivo has not been much investigated. We therefore compared the genome occupancy of Drosophila CBP (also known as nejire) with that of 40 different transcription factors in early Drosophila embryos.[23] Since Drosophila only has one p300/CBP ortholog, and the gene regulatory networks that control early embryo development are among the best characterized, this system provides an excellent opportunity to investigate if there is a preference for some transcription factors over others in determining genome occupancy of p300/CBP. We found that Drosophila CBP co-occupies the genome with the Rel-family transcription factor Dorsal, a homolog of vertebrate NF-κB, to a larger extent than any other factor.[23] Dorsal is the key activator of dorsal-ventral patterning in Drosophila, and forms a nuclear concentration gradient from ventral to dorsal.[26] In mutant embryos where Dorsal cannot enter the nucleus, around one-third of the CBP peaks change in intensity. CBP occupancy is reduced or lost at regions where Dorsal, but few other factors are bound in wild-type embryos, but remains unchanged at regions co-occupied by many factors. Thus, Dorsal is required for CBP occupancy in the early embryo, but only at regions where few other factors bind.[23]

In mutant embryos lacking Dorsal in the nucleus, CBP occupancy is instead best correlated with the co-Smad Medea, a Smad4 homolog that is a transducer of transforming growth factor-β (TGF-β) signaling.[27] The dorsal side of the embryo is patterned by Decapentaplegic (Dpp), a TGF-β signaling molecule of the bone morphogenetic protein (BMP) type. Without Dorsal protein, the entire embryo is converted into dorsal ectoderm, the tissue where Dpp-signaling occurs. This way, Dpp-signaling and Smad occupancy occurs in the entire mutant embryo, providing a genetic background in which CBP and Smad co-occupancy can be more easily detected.[23] These results show that CBP is most strongly associated with the two key dorsal-ventral patterning systems in Drosophila embryos, the Dorsal and Smad gene regulatory networks.

By contrast, transcription factors involved in anterior-posterior patterning, such as Bicoid and Caudal, overlap the CBP-binding regions to a much smaller extent. Although CBP has been shown to bind both Bicoid and Dorsal in vitro, and to stimulate both Bicoid and Dorsal activity in cell culture assays,[28-30] CBP co-occupies the genome much more strongly with Dorsal than with Bicoid in vivo.[23] This shows that Drosophila CBP has a preference for associating with some transcription factors and regulatory regions.

High occupancy target (HOT) regions are genomic sites bound by multiple factors, and are assigned a HOTness value depending on the number of factors and number of sites for each factor in that region.[31] Despite binding multiple different types of transcription factors, HOT regions can function as tissue-specific developmental enhancers driving gene expression patterns in selected cells.[32] In the Drosophila embryo, many of the CBP peaks overlap a HOT region.[23] However, the strongest CBP peaks are not found in the HOTest regions. Therefore, although the presence of multiple transcription factors can function as a platform for recruiting CBP, the specific factors present are important determinants of CBP occupancy. Together, these studies in Drosophila suggest that CBP recruitment depends on the presence of select transcription factors, and is not equally influenced by every factor.

Similarly, studies in mammalian cells suggest that p300/CBP occupancy depends on cell-type specific transcription factors, since tissue-specific ChIP experiments identify unique p300/CBP binding regions.[21] There is a dramatic redistribution of p300/CBP across the genome upon, for example, mitogen or estrogen stimulation, indicating that occupancy is influenced by what transcription factors are active.[33,34] Interestingly, early studies on p300 in mammalian cells indicated that p300 shows a preferential affinity for specific DNA sequences, namely those recognized by NF-κB.[35] Association of CBP with the NF-κB protein Dorsal in Drosophila, and p300 with NF-κB sequences in mammalian cells indicates that this preference is evolutionarily conserved.

Silent Genes Bound by p300/CBP are Hypoacetylated

It has been shown that H3K27ac distinguishes active from poised enhancers.[36-38] With p300/CBP being responsible for H3K27 acetylation, it might be expected that poised or inactive enhancers would lack p300/CBP. Nonetheless, a large number of silent regions bind p300/CBP,[37,38] while histone acetylation levels remain low.[23] This means that p300/CBP occupancy is not sufficient for gene activation, and that the HAT activity may be blocked at such sites (**Fig. 1A**). Poised enhancers can be subdivided into those containing Polycomb-related H3K27me3 and those lacking both H3K27me3 and H3K27ac.[38] Both types of enhancers can be occupied by p300/CBP. Thus, although H3K27me3-decorated chromatin restricts DNA accessibility,[39] it does not preclude p300/CBP binding. However, histone acetylation is prevented. Interestingly, all histone acetylations measured are blocked by H3K27me3-chromatin, not only the mutually exclusive H3K27ac.[23] This indicates that despite the ability of p300/CBP to bind to genes enclosed in H3K27me3-chromatin, the histones are not accessible for acetylation by p300/CBP and other HATs. These data are consistent with a model for Polycomb silencing that allows access of proteins and RNAP II to DNA, but that restrains RNAP II elongation.[40]

Regulation of p300/CBP Activity

The ability of H3K27me3-chromatin to preclude H3K27 acetylation by p300/CBP provides one mechanism for regulating the HAT activity of these proteins. Except substrate availability, other mechanisms may also be at work. For instance, poised enhancers lacking H3K27me3 can be occupied by p300/CBP but this does not result in H3K27 acetylation. Similarly, in the Drosophila embryo, the *twi* promoter contains less histone acetylation in the neuroectoderm than in the

dorsal ectoderm despite less amounts of H3K27me3 and similar levels of CBP occupancy.[23] Together, these results indicate that the HAT activity of p300/CBP is not only regulated by substrate availability, but also by genomic context or signaling. For example, methylation of CBP by CARM1 has been shown to increase the HAT activity in vitro,[34] and WTX may increase CBP-mediated acetylation of p53.[41] Phosphorylation of p300/CBP is also known to regulate both the stability and activity of the proteins.[42] Autoacetylation of p300/CBP enhances the catalytic activity of these proteins, but whether autoacetylation is regulated is not known.[43]

In addition to the HAT activity, p300/CBP have also been reported to display E3 and E4 polyubiquitin-ligase activities.[44,45] These functions are exclusively cytoplasmic and required for the rapid turnover of p53 in unstressed cells. However, since they do not occur in the nucleus, the ubiquitin-ligase activities do not directly influence target gene expression.

Balance of p300/CBP-mediated H3K27ac and Polycomb-mediated H3K27me3

Several studies have detected p300/CBP occupancy at silenced genomic sites carrying Polycomb-mediated H3K27me3.[23,37,38] In a wider meaning, these sites may be considered to be bivalent, as they harbor both an active feature (i.e., p300/CBP) and a repressed feature (H3K27me3). Given the ability of p300/CBP to acetylate H3K27, this hints at a role for p300/CBP in switching between an active and a repressed state. Indeed, a switching role between H3K27 acetylation and trimethylation in gene activation has been proposed both in mouse and Drosophila cells.[7,46] Perturbing H3K27ac by CBP knockdown or overexpression results in an antagonistic change in H3K27me3 in vivo.[7] In Drosophila, CBP binds to the H3K27-specific demethylase UTX, and co-occupies many Polycomb target genes together with UTX upon activation.[47] However, discrimination between a direct switching role for CBP and CBP occupancy as an indirect consequence of gene activity has not been possible.

What is the Function of p300/CBP at Regulatory DNA?

Once recruited to the genome, what is the function of p300/CBP at regulatory DNAs? In general, p300/CBP occupancy correlates with gene activation, even though p300/CBP recruitment does not always result in gene expression.[48] Although p300/CBP is found both at distal enhancer elements and at promoters, it is not known if p300/CBP exert different functions at promoters and enhancers. It is possible that p300/CBP is important for recruitment of RNAP II to promoters by interacting with basal transcription factors such as TFIIB and hypophosphorylated RNAP II.[49,50] Alternatively, p300/CBP-mediated acetylation of transcription factors or other proteins may facilitate RNAP II recruitment. At many inducible genes, acetylation of nucleosomes containing H3K4me3 is rapidly and continuously turning over in a p300/CBP dependent manner. This dynamic acetylation coincides with RNAP II association and gene activation.[51] In other cases, stimulation of cells leads to rapid recruitment of p300/CBP and RNAP II to the promoter where these factors persist for several hours, although transcription is transient.[33] This “bookmarking” allows for rapid re-initiation of transcription. Another possibility is that CBP facilitates transcription elongation, for example by controlling release form promoter-proximal pausing. It has been shown that p300 can acetylate and enhance the activity of positive transcription elongation factor b (P-TEFb), a major regulator of release from pausing.[52,53]

Conclusions

Genome-wide mapping of the p300 and CBP co-activators has shown that they are present at a large fraction of regulatory genomic regions, and that p300/CBP occupancy can therefore be used to identify enhancer sequences. Studies in Drosophila have shown that there is a preference for some transcription factors over others in directing p300/CBP to the genome. Since the amount of p300/CBP in cells is limiting,[54,55] only a subset of genes are targeted, leading to activation of specific gene regulatory networks.

A surprising finding is that although p300/CBP occupancy in general correlates with gene activation, they can also be found at silent regions. At these silent sites, p300/CBP occupancy does not cause histone acetylation, which may be one reason for why the corresponding genes remain silent. The histone acetylase activity of p300/CBP may be regulated, but one important mechanism for preventing H3K27ac at silent genomic regions is the antagonistic methylation of H3K27 by the Polycomb complex PRC2. Interestingly, although H3K27me3 is associated with repressive chromatin, it does not preclude p300/CBP binding, resulting in what may be considered a bivalent situation. The antagonism between H3K27ac and H3K27me3 indicates that p300/CBP may be important for switching between repressed and active chromatin states.

Although p300 and CBP have been extensively studied for almost 20 years, their exact function at both active enhancers and promoters as well as at poised and silent regions remains to be discovered.

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