

Regulation of gene expression by transcription factor acetylation

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Abstract. In the nucleus, DNA is tightly packaged into higher-order structures, generating an environment that is highly repressive towards DNA processes such as gene transcription. Acetylation of lysine residues within proteins has recently emerged as a major mechanism used by the cell to overcome this repression. Acetylation of non-histone proteins, including transcription factors,

as well as histones, appears to be involved in this process. Like phosphorylation, acetylation is a dynamic process that can regulate protein-DNA and protein-protein interactions. Moreover, a conserved domain, the bromodomain, has been implicated in the binding of acetylated peptides, suggesting a role for acetylation in intracellular signalling.

Key words. Acetyltransferase; histones; acetylation; transcription factors; gene expression; chromatin.

Introduction

During the last 25 years or so there have been major advances in understanding the regulation of gene transcription. Many of the important findings have utilised reconstituted *in vitro* systems, mostly using naked linear DNA as template. These studies have been very useful, providing a firm foundation for our understanding of gene transcription. However, *in vivo* the situation is considerably more complex. In the nucleus DNA is packaged into higher-order, stable chromatin that is very repressive to DNA processes such as transcription, replication, repair and recombination. The cell employs many different mechanisms to overcome this repression, one major mechanism being post translational modification of proteins. Here, we address the role of protein acetylation in regulating gene transcription. We describe the major advancements in our understanding of the importance of histone acetylation and how this led to the identification of the enzymes involved. The recent identification of non-histone substrates, which are predominantly transcription factors, and the implications with respect to transcription and intracellular signalling are discussed.

Histone acetylation

The nuclear environment is predominantly repressive towards transcription, with the DNA being packaged into stable higher-order structures. The basic unit of DNA packaging is the nucleosome, comprising approximately two turns of DNA duplex around a histone octamer core. Nucleation of the nucleosome is achieved when two dimers of (H2A/H2B) bind either side of a (H3/H4)₂ tetramer that is already complexed with DNA [1]. Addition of the linker histone H1 to this unit then allows the formation of higher-order chromatin, with the resultant tight packing of nucleosomes [2]. *In vivo* the modification of histones by acetylation was originally reported by Allfrey et al. in the 1960s [3]. Subsequently, it was shown that histone acetylation correlated with regions of transcriptional activity, and conversely hypoacetylated regions of the genome appeared to be generally transcriptionally inert [4–6]. The fundamental importance of histone acetylation *in vivo* was strongly implied from genetic approaches. For instance, mutation of lysines to glutamine within the N-termini of yeast histones H3 and H4 (which is thought to mimic lysine acetylation) alleviated the need for transcriptional coactivators at certain genes [7–9]. The main sites of histone acetylation *in vivo* are now known (table 1). Noticeably, each histone is acetylated

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in its N-terminus on specific lysine (K) residues. Acetylation of these sites serves to neutralise the positive charge of the K, and this led to the suggestion that acetylation of histones would weaken the nucleosomal structure and thereby facilitate transcription. Recently, the crystal structure of a nucleosome was resolved to 2.8 Å, revealing some interesting features [10]. It showed that the histone N-terminal tails make only weak electrostatic contacts with the DNA superhelix, and the tails of H3 and H4 extend beyond their own nucleosome to make contacts with adjacent nucleosomes. In fact, biophysical analysis has indicated that internucleosome contacts of the core histone tails are more important for chromatin higher-order structure than stabilisation of the core particle itself [11, 12]. Acetylation of histone tails may thus serve to 'open' higher-order chromatin via disruption of nucleosome-nucleosome contacts; and since acetylation is a dynamic process, this disruption could be reversed by deacetylation of the histone tails.

Although histone acetylation is predominantly associated with gene activation, there are specific examples where acetylation appears to be required for silencing, for example at telomeres. This repression mechanism has been extensively studied in yeast and appears to be dependent upon the acetylation of histones, since loss of a deacetylase, RPD3, leads to an increase in gene silencing at telomeres [13]. However, it should be noted that acetylation correlating with silencing is the exception rather than the rule. In the vast majority of cases, acetylation correlates with increased gene activity.

Identification of acetyltransferases

Until relatively recently, very little was known about the nuclear enzymes that acetylated histones. A major advance was made by Allis and co-workers with the identification of the first nuclear histone acetyltransferase

(HAT), p55 from *Tetrahymena* [14]. This enzyme was found to be homologous to yeast GCN5 (yGCN5), a known transcriptional activator, and yGCN5 was soon shown to possess intrinsic HAT activity. This was the first indication that transcriptional coactivators might function via the modification of histones. Mammalian coactivators, such as CBP and its homologue p300, were also shown to possess intrinsic HAT activity, underscoring the importance of this activity in gene transcription throughout evolution [15, 16]. There are now several reported families of acetyltransferases, exemplified by PCAF/GCN5, p300/CBP, TAF_{II}250, SRC1 and TIP60 (reviewed in [17]). Table 2 lists the currently identified HATs and the substrate specificity of the enzyme, if known. Interestingly, coactivator HATs appear to complex with other HATs. For example, CBP/p300 binds PCAF and SRC-1 [18, 19]. This may be an indication of promoter specificity, i.e. a given promoter may be optimally transcribed only when the appropriate combination of HATs (and therefore the appropriate pattern of histone acetylation) are present, the combination of HATs being determined at least in part by specific DNA-binding transcription factors bound to the promoter. Indeed, this would explain the abundance of distinct HATs.

As discussed above most nuclear HATs identified to date are transcriptional coactivators. However, this is not the case for all HATs. The TATA-box-binding basal transcription factor TFIID is composed of the TATA-binding protein (TBP) and numerous other tightly associated factors (TAF_{II}s) [20]. The largest of these TAF_{II}s, TAF_{II}250, harbours intrinsic HAT activity [21] that may facilitate TFIID binding to promoters and/or makes the promoter accessible to other factors. Once RNA polymerase II (RNA pol II) has been recruited to a promoter, transition from transcriptional initiation to elongation occurs. The elongation complex contains RNA pol II in addition to numerous accessory factors. In yeast, one such accessory factor is Elp3,

Table 1. Sites of histone acetylation in vivo

H4	S	G	R	G	^{Ac} K 5	G	G	^{Ac} K 8	G	L	G	^{Ac} K 12	G	G	^{Ac} A 16	K	R	H	R	K	V	L	R	D	N
H3	A	R	T	K	Q	T	A	R	^{Ac} K 9	S	T	G	G	^{Ac} K 14	A	P	R	^{Ac} K 18	Q	L	A	T	^{Ac} K 23	A	A
H2A	S	G	R	G	^{Ac} K 5	Q	G	G	^{Ac} K 9	A	R	A	K	A	K	T	R	S	S	R	A	G	L	Q	F
H2B	P	E	P	A	K	S	A	P	A	P	K	^{Ac} K 12	G	S	^{Ac} K 15	K	A	V	T	^{Ac} K 20	A	Q	K	^{Ac} K 24	D

Table 2. HATS and their substrates.

HAT	Complex	Organism	Substrates
Gcn5	–	<i>S. cerevisiae</i>	H2B, H3 (K14), H4 (K8, K16)
Gcn5	Ada	<i>S. cerevisiae</i>	<i>H2B*</i> , <i>H3</i>
Gcn5	SAGA	<i>S. cerevisiae</i>	<i>H2B</i> , <i>H3</i>
p55	–	<i>Tetrahymena</i>	H2B, H3, H4
P/CAF	–	<i>D. melanogaster</i>	H3
P/CAF	PCAF	<i>H. sapiens</i>	H3, p53(K320), P/CAF, HMG I(Y)(K71), HMG-17 (K2)
			TFIIE- β , TFIIF
			H3
hGCN5	TFTC	<i>H. sapiens</i>	
yTAFII130	TFIID	<i>S. cerevisiae</i>	
hTAFII250	TFIID	<i>H. sapiens</i>	H3 (K14), H4, TFIIE- β
CBP	–	<i>H. sapiens</i>	<i>H2A</i> , <i>H2B</i> , <i>H3</i> , <i>H4</i> (K5, K9, K12, K16), TFIIE- β , TFIIF, p53 (K382), GATA-1, EKLF, dTCF, HMG I(Y)(K65), CBP, PC4, Rch1
p300	–	<i>H. sapiens</i>	<i>H2A</i> , <i>H2B</i> , <i>H3</i> , <i>H4</i> (K5, K9, K12, K16), TFIIE- β , TFIIF, p53 (K382), GATA-1, EKLF, p300, PC4, Rch1
ACTR	–	<i>H. sapiens</i>	<i>H3</i> , <i>H4</i>
SRC-1	–	<i>H. sapiens</i>	<i>H3</i> (K9, K14), <i>H4</i>
ESA1	–	<i>S. cerevisiae</i>	H2A, H3, H4
Tip60	–	<i>H. sapiens</i>	H2A, H3, H4
Elp3	elongator	<i>S. cerevisiae</i>	H2A, H2B, H3, H4

* Nucleosomal histones are set in italics.

which has recently been shown to possess HAT activity [22]; thus, HAT activity appears necessary both for efficient initiation and also for subsequent elongation in vivo.

Following the identification of the actual acetyltransferase enzymes, the complexes within which they reside have begun to be characterised. The identification of proteins within these complexes led to the surprising observation that TAF_{II}250 associated factors from the TFIID complex (i.e. other TAF_{II}s) are also found in the human P/CAF and GCN5 complexes, as well as yeast TAF_{II}s being identified in the yeast GCN5 complexes [23–25]. Strikingly, the majority of these TAF_{II}s are ones that bear structural similarity to histones. This is presumably an indication of a common functional requirement of these complexes that has yet to be convincingly identified.

Acetylation of non-histone substrates

The identification of novel HATs prompted the question whether the same enzymes could acetylate other, non-histone proteins. Recent evidence has indicated that this is indeed the case and has led to many HATs being redefined as factor acetyltransferases (FATs). Broadly speaking, the non-histone substrates can be divided into three categories (i) architectural DNA binding factors, (ii) basal transcription factors and (iii) site-specific DNA binding factors (table 2).

Acetylation of architectural DNA binding factors

In the cell there are many non-histone proteins which are involved in DNA structure. One class of such proteins is the high-mobility group (HMG), which consists of three sub-groups [26]. Those containing an HMG-box DNA binding domain (DBD), e.g. HMG1 or SRY, bind DNA via the minor groove and bend their target DNA; they have been implicated in both differentiation and transcription. The second HMG subgroup is the I/Y/I-C proteins which contain three short (nine residues) DBDs that also bind in the minor groove but have only a limited effect on DNA conformation.

During viral infection a stable higher-order nucleosomal complex forms at the virus-inducible enhancer of the interferon β (IFN- β) gene. This complex is called an enhanceosome and requires the high-mobility-group protein HMG I(Y) both for assembly and maintenance [27]. CBP and P/CAF are recruited to this complex and lead to activation of the IFN- β gene, and both CBP and P/CAF have been shown to acetylate HMG I(Y), though at different sites [28]. Acetylation of HMG I(Y) by CBP occurs at K65, which is immediately adjacent to the second DBD; this decreases the DNA binding ability of HMG I(Y) and leads to enhanceosome disruption. This effect is required for the postinduction turn-off of the IFN- β enhanceosome. However, the consequences of acetylation of HMG I(Y) at K71 by P/CAF have not yet been established. Thus, the acetyltransferase activity of CBP, but not P/CAF, is essential

to switch off enhanceosome activity following viral activation. CBP acetyltransferase activity is not only required for IFN- β gene turn-off but is also essential for full viral induction of the IFN- β gene, as is P/CAF acetyltransferase activity. In addition to acetylation of HMG I(Y), histones H3 and H4 at the hIFN- β promoter also become hyperacetylated in a CBP-dependent manner following viral infection [29]. Taken together, these observations suggest a two-step mechanism for viral induction of the IFN- β gene: First, viral induction leads to enhanceosome formation and recruitment of CBP and P/CAF, which together acetylate histones H3 and H4, leading to gene activation. Postinduction however, CBP but not P/CAF acetylates HMG I(Y), leading to enhanceosome destabilisation and ultimately IFN- β gene inactivation. P/CAF has also been demonstrated to acetylate HMG-17, a member of the third HMG subgroup that binds to nucleosomal structures and unfolds higher order DNA structures [30]. Acetylation of HMG-17 by P/CAF occurs at K2 in vitro, a site known to be acetylated in vivo. Acetylated HMG-17 binds to nucleosomal cores with reduced affinity compared with that of unacetylated HMG-17, but the effect of this modification upon gene transcription has yet to be determined.

Acetylation of general transcription factors

General transcription factors, together with RNA pol II, give rise to basal gene transcription. To date, two of the general transcription factors have been shown to be acetylated, at least in vitro. They are the β subunit of TFIIE and, to a lesser extent, both subunits of TFIIIF [31]. All three acetyltransferases analysed (p300, P/CAF and TAF_{II}250) were found to acetylate TFIIE- β , whereas only P/CAF and p300 acetylated TFIIIF. These modifications, and their effects, have yet to be demonstrated in vivo.

In in vitro transcription assays, the basal transcription factors require additional factors in order to give rise to activated gene transcription. One such factor is the upstream stimulatory activity (USA) cofactor fraction [32, 33]. USA itself is composed of numerous factors, both positive and negative with respect to regulating transcription. One positive cofactor is the PC4 protein that is acetylated by CBP, at least in vitro (A. Bannister and M. Meisterernst, unpublished). The consequences of this modification are not known, although one could speculate that it allows PC4 to more actively promote transcription.

Acetylation of site-specific DNA binding factors

Gene expression in the eukaryotic cell is regulated by site-specific DNA binding factors. These specific tran-

scription factors have two separable functions. First, they must bind to promoter or enhancer elements of target genes and, second, modulate transcription from these genes. Both steps have been shown to be regulated by posttranscriptional modification of the specific transcription factor itself. Phosphorylation has been by far the most studied of those modifications; however, glycosylation has also been described [34, 35]. Acetylation of non-histone substrates by HATs and their link to transcription suggests that acetylation of specific transcription factors might also regulate their activity.

The first site-specific DNA binding factor shown to be acetylated was the tumour suppressor protein p53 [36–38]. p53 is acetylated on lysines K320 and K382 in vivo. These sites correspond to lysines targeted by p300 (K382) and P/CAF (K320) in vitro. Both HATs have previously been shown to be coactivators of p53 [39]. K382 is located in the C-terminal regulatory region of p53 which also harbours sites of phosphorylation and glycosylation. K320 is part of the nuclear localization signal. Acetylation of p53 by p300 and P/CAF in vitro increase its DNA binding activity, thus acetylation of p53 might be important for p53 function in vivo. One of the roles of p53 in the cell is thought to be the response to DNA damage from ionizing radiation (IR) or ultraviolet light (UV). Both insults result in the activation of p53 DNA binding activity and activation of p53 target genes, resulting in cell cycle arrest or apoptosis. Interestingly, p53 acetylation on both sites was found after cells were irradiated with IR or UV [37, 38]. Since p53 acetylation occurs after p53 phosphorylation, these two events may be linked. The data so far suggest that p53 acetylation is regulated and has a measurable effect on p53 activity in vitro. However, both the true in vivo p53 acetyltransferase and its requirement for p53 function remain to be established.

p53 was joined very soon by other specific transcription factors that were found to be acetylated. The erythroid Krüppel-like factor (EKLF) is a red-cell-specific transcription factor involved in erythroid ontogeny. It was demonstrated to be acetylated in vitro and in vivo [40]. CBP and p300, but not P/CAF, are able to acetylate EKLF in vitro. A function for EKLF acetylation has not so far been established. Another transcription factor from the haematopoietic lineage, GATA-1, is also acetylated in vivo, and by CBP and p300 in vitro [41, 42]. Mutation of the lysines that are acetylated in GATA-1 results in a decreased transcriptional activation capacity. The acetylated region of GATA-1 falls into a highly conserved region that is also required for megakaryocyte differentiation.

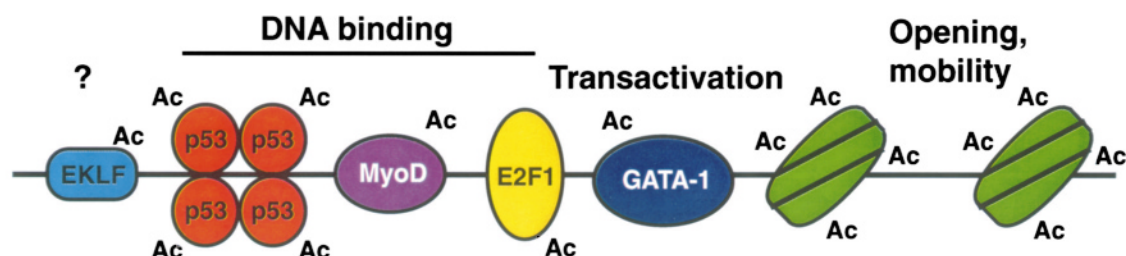
The myogenic transcription factor MyoD has also been shown to be acetylated in vivo [43]. In vitro, P/CAF but not CBP acetylates MyoD and the acetylation was shown to increase the DNA binding activity of MyoD. Mutation of the acetylated lysines impairs the myogenic potential of MyoD in a tissue culture differentiation system. Like MyoD, the DNA binding activity of the cell-cycle regulator E2F1 is also increased via acetylation [43a]. The stability of the E2F-1 protein is also increased through acetylation [M. Martinez-Balbas et al., submitted]. E2F-1 is acetylated in vivo and acetylated preferentially by P/CAF in vitro.

All factors described above demonstrate a positive effect of acetylation on transcriptional activity. The opposite is proposed for the *Drosophila* T cell factor (dTCF).

dTCF is an HMG-box-containing transcription factor acting downstream of Wnt/Wingless signalling [44]. Association with the coactivator β -catenin/Armadillo stimulates its activity. Acetylation of dTCF by dCBP in vitro lowers dTCF affinity for β -catenin/Armadillo and this negative effect of dTCF acetylation correlates with the observation that dCBP mutants show a Wnt/Wingless overactivation phenotype. Acetylation of dTCF in vivo remains to be established.

Very recently, a negative role towards transcription was proposed for the acetylation of an actual HAT enzyme. The HAT, and nuclear hormone receptor coactivator ACTR, is acetylated by CBP, and this modification leads to the disruption of the nuclear hormone receptor:coactivator complex [45].

Acetylation stimulates



Acetylation inhibits

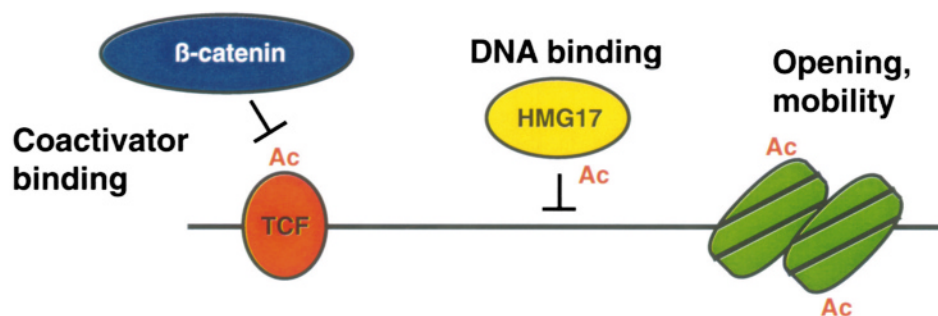


Figure 1. Factor acetylation regulates transcription. Acetylation has both positive and negative effects on transcription. Known examples are summarised. Notably, acetylation of nucleosomal histones may have both positive and negative effects on nucleosome mobility, factor accessibility and heterochromatin assembly.

The diversity of examples of specific transcription factors shown to be acetylated to date (summarized in fig. 1) suggests that they are just the tip of the iceberg and that we can expect to find more in future. So far, factors involved in DNA damage, differentiation and development have been identified. Factor acetylation seems to modulate DNA binding, association with cofactors and possibly transactivation. In addition, proteins not directly involved in regulating transcription have also been shown to be acetylated by transcriptional coactivators. An example is the nuclear import factor Rch1, which is an importin- α isoform that recognises classical nuclear localisation signals (NLSs) and functions as an import adapter allowing access to the importin- β -dependent import pathway. CBP/p300 acetylates Rch1 at K22 *in vitro*, a site which is acetylated *in vivo* [50]. Presumably this modification of Rch1 somehow regulates its function in nuclear import, a process that could obviously effect changes in gene expression. Although *in vivo* mechanisms and functions remain to be analysed for all acetylated substrates, a common theme is emerging: all specific transcription factors share the ability to bind to their specific acetylase.

Autoacetylation of acetyltransferases

Protein modification enzymes often modify themselves, and acetyltransferases are no different. Auto- (or cross-) acetylation has been reported for both CBP/p300 and P/CAF [46, 47]. P/CAF is autoacetylated in its N-terminus, and enzyme kinetic studies have led to the suggestion that the modification may somehow respond to the ratio of coenzyme A (CoA) to acetyl-CoA within the cell [46]. Thus, P/CAF HAT activity may be regulated in this manner, and the regulation would be specific to P/CAF since human GCN5 (hGCN5; a homologue of P/CAF) does not autoacetylate. Hence the ratio of CoA to acetyl-CoA could specifically regulate P/CAF but not hGCN5. Perhaps this mechanism is used by the cell to independently regulate the activity of P/CAF and hGCN5. Mapping of the P/CAF autoacetylation site shows it to be located within a basic N-terminal region that acts as a nuclear localisation sequence when transposed in-frame to a heterologous nonnuclear protein [M. Martinez-Balbas and T. Kouzarides, unpublished observation]. This opens the possibility that the cellular compartmentalisation of P/CAF may be regulated via autoacetylation. At present there is no known role for the acetylation of CBP/p300. Identification of the amino acid(s) modified may help to suggest a possible role, but it is probable that these acetylation reactions occur to somehow regulate the function of the associated acetyltransferase activity.

Acetyltransferase specificity

As discussed above, there is now a growing list of substrates for acetyltransferases. However, comparison of primary amino acid sequences surrounding each site of acetylation has revealed surprisingly little concerning consensus sequences of substrates. One exception is a consensus acetylation site for yeast GCN5; yGCN5 acetylates targets with the consensus K-X-X-G-G/A-K-X-not G-X-K/R reviewed in [48]. However, genetic evidence indicates that yGCN5 may have a broader substrate specificity *in vivo* since a non-H3/H4 acetylation activity of yGCN5 is essential for viability if the yGCN5 acetylation sites within H3 and H4 are removed [7]. Of course, this could be due to yGCN5 acetylating H2A and/or H2B, or the enzyme may acetylate non-histone targets *in vivo*.

The crystal structure of Tetrahymena GCN5 bound to Co-A and a histone H3 peptide was recently solved [49], indicating that a short recognition sequence within H3 (G-K-X-P) contains the primary binding determinants of GCN5. The K residue within this sequence is the one that is acetylated. This is consistent with the sequences within the nuclear import factor Rch1, which are required for acetylation by CBP [50]. Here, as for GCN5, a G-K motif is essential for CBP-dependent acetylation. It is worth noting that the substrate specificity of purified HATs may not directly reflect that found *in vivo*. For example, purified yGCN5 can acetylate free histones but not nucleosomal histones [14]. However, when purified from yeast as part of the large ADA or SAGA complex, yGCN5 can acetylate nucleosomal histones [51]. This property again emphasises the importance of protein:protein interactions in regulating HAT activity and consequently the transcriptional activity of responsive genes.

Regulation of HATs

Transcription of target genes is regulated locally through recruitment of specific DNA-binding transcription factors. The activated transcription factor then recruits coactivators such as HATs. In this model the transcription factor itself is the endpoint of intracellular signaling, which allows the specific regulation of target genes. There is, however, an alternative mode of regulation, namely at the level of the coactivator, and there exists an increasing amount of evidence that signalling to the coactivator can be important for transcriptional activation [52, 53].

With several co-activators now being identified as HATs, it became possible to test whether intracellular signalling would directly affect the HAT activity of these co-activators. The first indication came from human GCN5 (hGCN5). hGCN5 was demonstrated to be

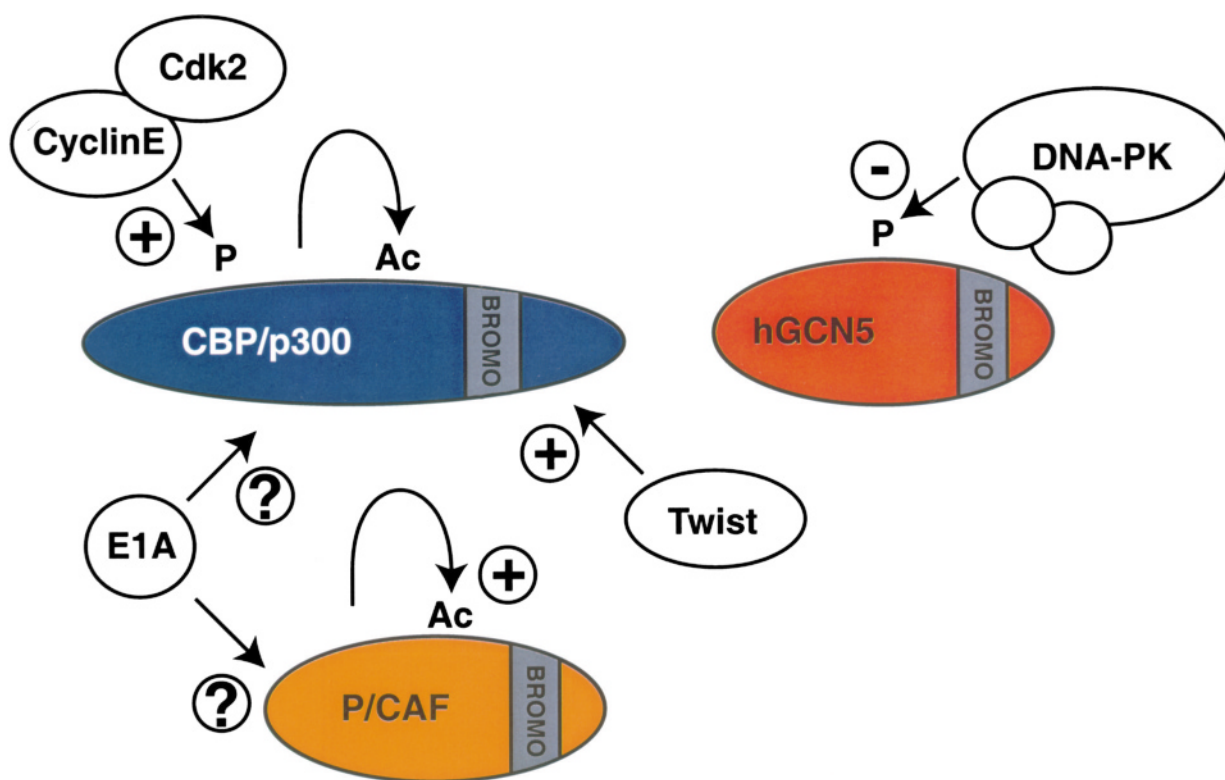


Figure 2. Regulation of acetyltransferase activity. Both posttranslational modification and factor binding have been proposed to regulate acetyltransferase activity.

phosphorylated by the DNA-dependent protein kinase (DNA-PK), and this phosphorylation inhibited hGCN5 HAT activity [54]. This finding demonstrated that HAT activity could be regulated by posttranslational modification of the HAT itself and also suggested a putative role of GCN5 in response to DNA damage. The precedent being set, this study was followed by a cell-cycle analysis of CBP HAT activity [55], which was found to vary with a peak of activity at the G1/S transition. This peak coincided with an increase of CBP phosphorylation. Although the *in vivo* kinase responsible for this phosphorylation remains to be determined, the authors found that phosphorylation of CBP *in vitro* by cyclinE/cdk2 increases its HAT activity.

The adenovirus oncoprotein E1A appears to be able to mimic the activating effect of phosphorylation [55]. This is consistent with earlier findings that showed CBP bound to E1A was active and that expression of E1A in cells increased CBP HAT activity [15]. In addition, E1A binding to P/CAF does not affect HAT activity [56]. However, these findings are in contrast to

two more recent reports [47, 57], both of which identify E1A as a negative regulator of both CBP/p300 and P/CAF HAT activity. Furthermore, they demonstrate a negative role of E1A on p300-dependent transcription. Hamamori et al. also identify a cellular protein, the basic helix-loop-helix protein twist, which shares the inhibitory effect of E1A [57]. This apparent discrepancy may be due to the fact that E1A can regulate transcription both positively and negatively, and the different studies may have a different mechanistic bias towards these alternative modes of operation.

Although the controversy around the effect of E1A on HAT activity remains to be resolved, the data so far suggest that HAT activity can be modulated by phosphorylation and/or via association with regulatory proteins. Thus, intracellular signalling is also directed towards HATs. The rationale behind this type of control might be the coordinate regulation of a subset of genes that are dependent on HAT function, independent of their specific promoter or enhancer composition. A summary of the regulation of various HATs is shown in fig. 2.

Acetylation and intracellular signalling

As mentioned above, the interaction of dTCF and Armadillo may be regulated by acetylation of dTCF [44], i.e. protein acetylation might regulate protein-protein interactions. This suggests that protein domains might have evolved to recognise acetylated versus nonacetylated proteins. Such a recognition motif would be comparable to SH2 domains, which specifically interact with certain proteins only if they carry a phosphorylated tyrosine. Such a function has recently been proposed for the bromodomain, which is found in many HATs such as CBP/p300 and P/CAF [58]. Using structural analysis and site-directed mutagenesis, this study demonstrates that the bromodomain interacts specifically with acetylated histone tails. Thus, in the same way that many kinases carry SH2 domains, HATs might carry acetylation-specific protein interaction domains. Moreover, as mentioned above, HATs are auto-modified in a similar way to kinases. In addition, certain HATs may contain domains that specifically target and bind nonacetylated sequences. Given these data, one could speculate that, like phosphorylation, acetylation has a wider role in signal transduction. This new kind of signalling would involve HATs, bromodomains and non-histone targets, in addition to histones. The players have been identified, it now remains to establish the rules of the game.

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