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Point of View

# Histone acetylation

## Where to go and how to get there

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**Transcriptionally active DNA is packaged with histones that are post-translationally acetylated on multiple lysines within their amino termini. While the majority of this acetylation is limited to the promoters of genes, acetylated histones are also found throughout transcribed units. Over the last decade we have uncovered many of the pathways involved in directing histone acetylation to active genes. This review will summarize much of this groundbreaking research as well as discuss some of the outcomes of this important protein post-translational modification.**



DNA is packaged as chromatin in the nucleus of eukaryotes by both histone and non-histone proteins. Chromatin plays a role in transcription, DNA repair and replication by remaining structurally dynamic. The basic unit of chromatin is the nucleosome, which is comprised of two copies each of histones H2A, H2B, H3 and H4 around which is wrapped 147 base pairs of DNA.[1] The amino terminal tails of histones are exposed on the surface of the nucleosome and serve as the main sites for histone post-translational modifications. About 50 years ago, Allfrey and colleagues recognized that histone proteins were both acetylated and methylated.[2] They also realized that acetylation was positively correlated with transcriptional activity. Since then, genome-wide approaches have confirmed this initial study, providing evidence that histone acetylation at promoters is a hallmark of actively transcribed genes.[3-5] Moreover, the levels of acetylation are positively correlated with transcription rates.[3,4,6] In addition to promoter acetylation, lower levels of acetylation exist throughout the genome.[3,4] While a great deal of effort has been put into determining where acetylation is and its downstream effects, how exactly acetylation is targeted to many regions is not conclusively known.

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Histone acetyltransferases (HATs) exist as multi-subunit complexes generally consisting of a catalytic subunit and auxiliary proteins that are required for enzymatic activity and targeting. At least nine HAT complexes have been characterized in the yeast *Saccharomyces cerevisiae*.[7] Most HAT complexes preferentially modify specific lysine residues within either the H3 or H4 tails and many HATs have overlapping targets.[8-12] For example, Gcn5p, the catalytic subunit of at least three HAT complexes, SAGA, ADA and SLIK/SALSA, preferentially acetylates H3K14.[10,13] The Sas3p-dependent NuA3 complex shares specificity for H3K14 but also acetylates H3K23.[11] Histone acetylation is largely targeted to promoters, however, low levels of "global" acetylation are also found throughout transcribed genes. While promoter-localized acetylation has received a great deal of attention, little is known about the function of global acetylation. Here we will present a comparison of promoter-localized versus global acetylation and speculate on the possible functional differences between the two, focusing on the yeast *S. cerevisiae*.

## Promoter-Localized Acetylation

Initial work on promoter-localized acetylation began when the *Tetrahymena* homolog of the yeast transcriptional co-activator, Gcn5p, was found to have acetyltransferase activity.[14] Shortly after, it was shown that Gcn5p is directed to target gene promoters by the transcriptional activator Gcn4p, and that acetylation by Gcn5p is required for gene activation showing a role for acetylation in transcriptional activation.[15,16] Gcn5p is a component of the SAGA complex, which has been shown to interact with multiple transcriptional activators via its subunit, Tra1p.[17,18] Tra1p is also a component of the NuA4 HAT complex, which contains the catalytic subunit Esa1p.[19] SAGA and NuA4 seem to be the two main HAT complexes involved in transcriptional activation through promoter-targeted acetylation in yeast.[20,21] Unlike SAGA, which is a histone H3 specific HAT, NuA4 has specificity towards four lysines on the histone H4 tail.[19] While both HAT complexes appear to be involved in pre-initiation complex (PIC) formation they may do this via two distinct but not entirely unrelated pathways.

After recruitment through interaction with transcriptional activators both SAGA and NuA4 facilitate binding of the TATA-box

binding protein (TBP).[22,23] The importance of histone acetylation in PIC formation is underscored by the fact that aberrant acetylation can trigger transcriptional initiation from cryptic promoters within coding regions in yeast.[24] Acetylation of histone H3 by SAGA may promote TBP binding by increasing transient nucleosome unwrapping or enhancing histone octamer mobility as this modification has been shown to cause such effects in vitro.[25,26] Additionally, acetylated H3 has been shown to be a binding target of the bromodomain, a well characterized acetyl-lysine binding motif.[27] Bromodomains are found in both the SWI/SNF and RSC (Remodels the Structure of Chromatin) chromatin-remodeling complexes, which use the energy of ATP hydrolysis to alter chromatin structure by removing or sliding the histones away from the transcriptional start site.[28] In the case of RSC, acetylation of H3K14 plays a particularly important role in mediating nucleosome remodeling by this complex.[25,29] Thus the main role of H3 acetylation in PIC formation seems to be via direct or indirect alteration of nucleosome structure, facilitating access of the transcriptional machinery to nucleosomal DNA (Fig. 1, right).

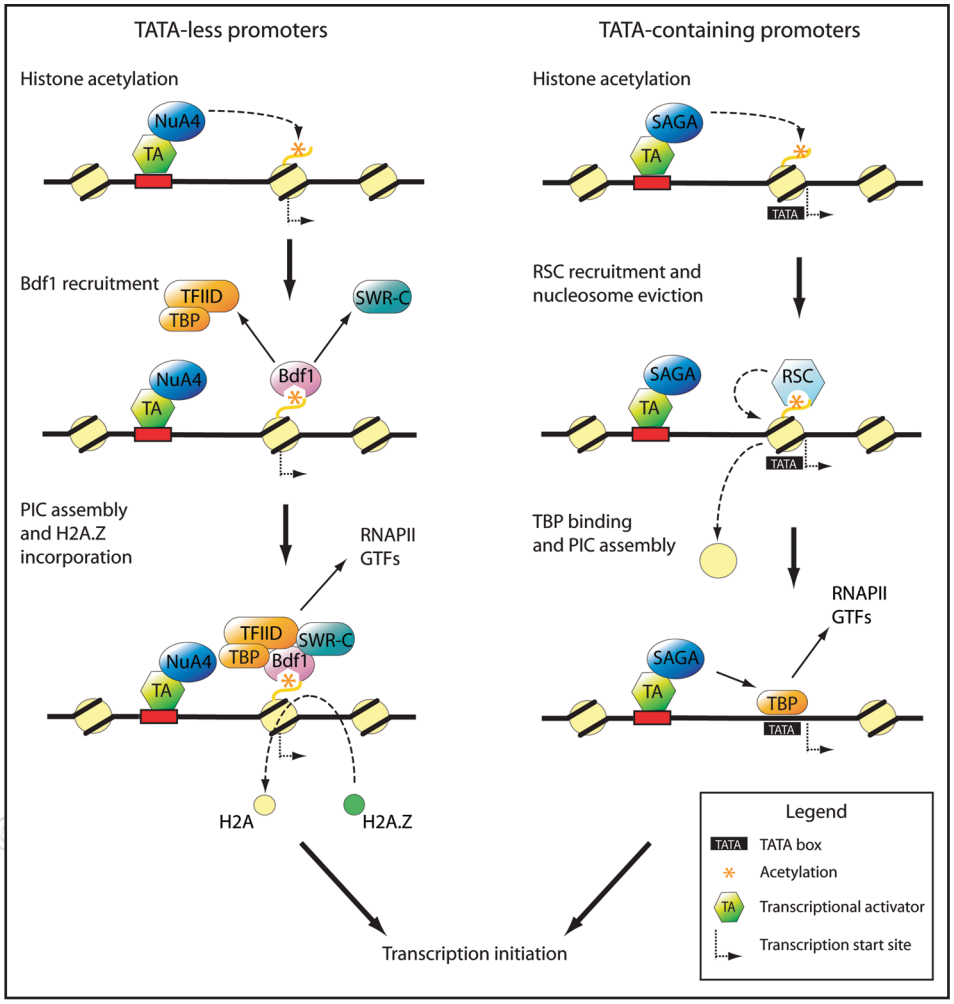


Figure 1. Model for promoter targeted acetylation. Left side: At TATA-less promoters, NuA4 associates with promoter regions via interaction with a transcriptional activator (TA) and acetylates histone H4 (*). Bdf1p binds to this acetylation mark and recruits TFIID and SWR-C. This leads to PIC assembly, replacement of canonical H2A with H2A.Z and transcription by RNAPII. Right side: At TATA-box containing promoters, SAGA associates with promoter regions in a similar manner as NuA4 but acetylates histone H3. RSC (or SWI/SNF) binds this acetylation resulting in chromatin remodeling and exposure of the TATA box. TBP binds DNA at the TATA box leading to PIC formation and transcription by RNAPII.

In contrast, acetylation of H4 by NuA4 may serve a more direct role in TBP binding. H4 acetylation provides a binding site for a bromodomain within the TFIID subunit, Bdf1p and the presence of Bdf1p and TFIID at promoter regions is dependent on Esa1p and acetylation.[20,30,31] Studies have found that Bdf1p, TFIID and Esa1p co-localize to similar regions of the genome and that Bdf1p action at these regions is not dependent on TFIID; thus, suggesting that Bdf1p binding to these regions is directing TFIID binding.[20] Consistent with this, promoters that lack a classical TATA-box appear to be more dependent on NuA4 acetylation than on SAGA (Fig. 1, left).[20,32]

In addition to mediating recruitment of TFIID, Bdf1p is part of SWR-C (Swi2/Snf2-related complex), a complex that uses the energy of ATP hydrolysis to exchange histone H2A for the variant H2A.Z.[33-35] H2A.Z occupancy is also positively correlated with histone H4 acetylation, and placement of this variant likely stimulates transcription initiation through chromatin destabilization.[20,36] Thus, while H4 acetylation may facilitate direct recruitment of TFIID, it can also target chromatin remodeling activities to promoters.

## Global Acetylation

While a great deal is known about promoter-targeted acetylation and its outcome on transcriptional initiation, less is known about global acetylation. Originally, global acetylation was referred to as the basal, non-targeted acetylation found throughout the genome; however, in more recent articles global acetylation is seen as the acetylation observed throughout the transcribed unit of genes.[37] In human T cells, H3K14ac, H3K23ac and H4K12ac—unlike most other acetylation marks—are found, in addition to promoter regions, throughout regions of transcription.[4] In yeast, H3 and H4 acetylation can be observed over large domains upon deletion of genes encoding histone deacetylases (HDACs).[37,38] The question is how did this global acetylation arrive in the first place?

One obvious mechanism for targeting acetylation to transcribed genes is via an interaction between HATs and elongating RNA

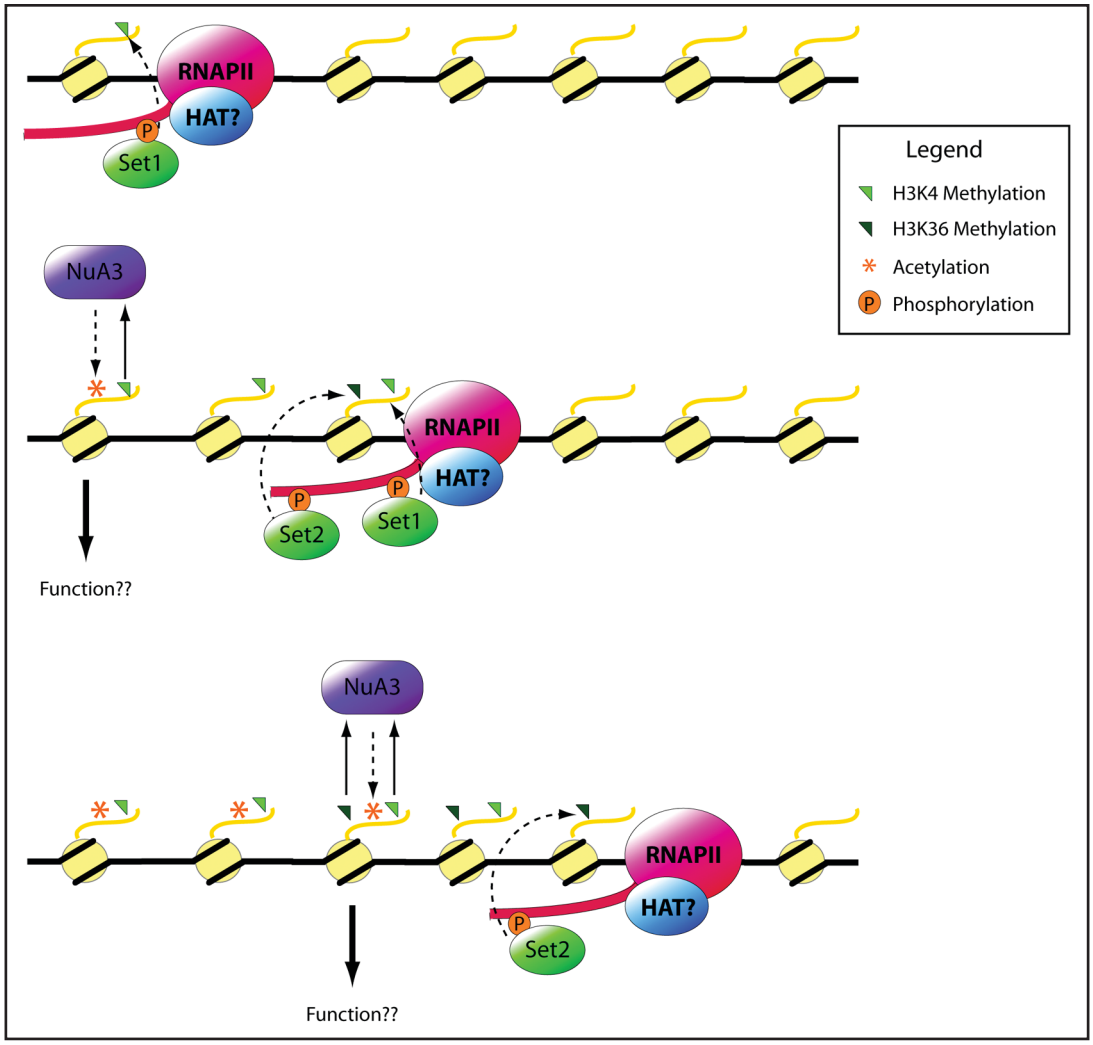


Figure 2. Model for global acetylation. Shown is RNAPII processing through a typical gene. At the 5' end of the transcribed region, Set1p interacts with the CTD of RNAP II which is phosphorylated at serine 5; thus, resulting in H3K4 methylation. As RNAP II progresses towards the 3' region of the gene, the CTD becomes phosphorylated at serine 2 recruiting the Set2p methyltransferase. The NuA3 HAT complex binds to histones that are methylated at H3K4 and/or H3K36 and acetylates H3K14. The function of this acetylation is unknown. A HAT complex such as SAGA (HAT?) may or may not associate with elongating RNAPII.

polymerase II (RNAPII). Consistent with this, a decade ago the Elongator complex was purified as a novel multi-subunit complex associated with elongating RNAPII.[39] One of the subunits, Elp3p, shares sequence similarity with the Gcn5p family of HATs and there has been evidence presented both in vitro and in vivo suggesting that Elp3p is a histone H3 HAT.[12,40] Additionally, deletion of *ELP3* results in defects in transcription of a subset of genes.[41] However, shortly after its discovery other groups have raised doubts as to the authenticity of Elongator as a HAT complex.

The question of whether or not Elongator is a bone-fide HAT complex stems from the difficulties in detecting Elp3p, not only at inducible genes but also at genes that are transcriptionally downregulated in the absence of Elp3.[42] This prompted the authors of this study to use immunofluourescence to determine the nuclear localization of Elp3p. Surprisingly, Elp3p was found to be primary cytoplasmic.[42] Additionally, Elongator has been shown to be required for modification of multiple non-histone substrates such as α tubulin[43] and tRNAs.[44] Of these, the most compelling evidence is for a role in tRNA modification as this was the only study to address Elongator's role in transcriptional elongation.[45] Overexpression of specific tRNA species can rescue histone acetylation and transcription elongation defects of *elp3*Δ strains.[45] While a direct role for Elongator in elongation remains questionable, other evidence suggests that RNAPII may target histone acetylation. In human cells the PCAF complex has been show to interact with the elongation-competent, phosphorylated form of RNAPII.[46] Additionally, SAGA, the yeast counterpart of PCAF, is found throughout the coding regions of multiple genes and this localization is dependent on phosphorylation of Ser5 of the carboxyl-terminal domain (CTD) of RNAPII; however, whether this is due to direct interaction between SAGA and RNAPII, remains to be shown.[47]

Another potential mechanism for recruiting HATs to transcribed genes is through H3K4 and K36 methylation. These

modifications are carried out by the histone methyltransferases Set1p and Set2p respectively.[48-50] These methyltransferases associate with phosphorylated Serine 5 (Set1p) and 2 (Set2p) of the CTD of RNAPII; thus elongating RNAPII leaves behind a trail of lysine methylation (Fig. 2).[51] These marks serve as docking sites for multiple chromatin-modifying complexes.

The NuA3 HAT complex acetylates both K14 and K23 of the histone H3 tail and its binding to chromatin requires both methylated H3K4 and H3K36 (Fig. 2).[11,52-54] Not surprisingly, NuA3 colocalizes with these marks throughout the genome.[54] The Yng1p subunit of NuA3 contains a PHD (Plant Homeodomain) finger which has been shown by several groups to be responsible for interaction with H3K4 methylation; however, the subunit which binds H3K36me is still unknown.[52,54-56] One of the mammalian counterparts of NuA3, the HBO complex, was shown to weakly interact with methylated H3K36 via the PHD finger of the JADE1 protein.[57] NuA3 has a JADE1 homolog, Nto1p, which was shown in vitro to bind methylated H3K36 via its PHD finger but no in vivo evidence for this interaction has been produced to date.[55] Additionally, it is not known whether other HATs are targeted in a similar manner. NuA4 contains Yng2p, which shares a highly conserved PHD finger with Yng1p and can bind H3K4 methylated histones in vitro.[55] Similarly, the SAGA complex has multiple motifs that have been implicated in H3K4me binding, although the presence of SAGA on coding sequences in yeast is independent of Set1p.[47,58] NuA4 and the Rpd3S HDAC complex share the subunit Eaf3p,[59-62] which preferentially interacts with H3K36me, however in the context of NuA4, Eaf3p is unable to bind H3K36me due to the absence of the Rpd3S subunit Rco1p.[63] Despite this however, the interaction of Esa1p with the *MET16* promoter is dependent on both H3K4 and K36 methylation.[64] Thus while the presence of histone acetylation marks within transcribed genes clearly indicates that HATs are targeted to these regions, how this is done has not been definitively determined.

While these studies suggest mechanisms by which HATs could be targeted to transcribed regions, the function of this acetylation remains somewhat of a mystery. It is plausible that acetylation of histones in transcribed regions is required for displacement of histones that pose a barrier to elongating RNAPII, and indeed multiple bromodomain-containing complexes such as SWI/SNF, SAGA and RSC have demonstrated functions in elongation.[47,65,66] However, the fact that most models suggest that histones are acetylated as RNAPII is passing through genes, is paradoxical.[67,68] Given that acetylation is thought to facilitate transcription why would acetylation be required after transcription has already occurred? Could this acetylation form some kind of transcriptional memory where subsequent rounds of transcription occur faster?

Nearly ten years ago, the Grunstein group looked at the effects of HDAC deletion on gene expression.[38] They found that in the absence of *RPD3* or *HDA1* the *PHO5* gene was slower to return to the repressed state after induction. More recently, the Peterson group examined *GAL* gene re-induction after transfer from galactose to glucose media, then back to galactose media again.[69] They did find that *GAL* genes are induced faster during the second induction suggesting there is some type of transcriptional memory involved. This transcriptional memory was found to be dependent on the SWI/SNF complex; however, it was not found to be dependent on Gcn5p or any of the methyltransferases. They did not, however, exclude the possibility that another or redundant acetyltransferases could be involved in this memory.

## Concluding Remarks

While a great deal of research has focused on the targeting of histone acetylation to promoters, the mechanism of establishment of low levels of acetylation at downstream regions is less well defined. Several recent studies point to a role for RNAPII-deposited histone H3K4 and K36 methylation in recruiting HATs to transcribed regions, although this has not been definitely shown. Additionally, the function of this type of acetylation is unclear. The idea that histone acetylation downstream of transcriptional start sites could be involved in subsequent rounds of transcription forming a "transcriptional memory" is appealing, and while there is evidence that this may not be the case for the *GAL* genes, it is still an intriguing possibility.

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