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Beyond the histone tail

Acetylation at the nucleosome dyad commands transcription

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Post-translational modifications (PTMs) of histones have been implicated in cellular processes such as transcription, replication and DNA repair. These processes normally involve dynamic changes in chromatin structure and DNA accessibility. Most of the PTMs reported so far map on the histone tails and essentially affect chromatin structure indirectly by recruiting effector proteins. A recent study by Schneider and colleagues published in *Cell*[1] has uncovered the function of H3K122 acetylation found within the histone globular domain and specifically positioned on the DNA-bound surface of the nucleosome. Their findings demonstrate a direct effect of histone PTMs on chromatin dynamics, and propose that modifications located in different parts of the nucleosome employ distinct regulatory mechanisms.

Keywords: chromatin, nucleosome, histone, post-translational modification, lateral surface, acetylation, transcription

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The genome in every eukaryotic cell is packaged into a macromolecular structure known as chromatin. Chromatin itself is composed of a repeating subunit—the nucleosome—that contains 147 bp of DNA wrapped around a protein octamer made up of two copies of each of the four histones H2A, H2B, H3, and H4. The accessibility of the DNA that is coiled around the histone octamer is a critical parameter for processes such as transcription, replication, recombination and DNA repair. Among various factors that control DNA accessibility, post-translational modifications (PTMs) of histones are key players since they regulate nucleosome dynamics.[2]

Numerous histone PTMs have been discovered to date, including acetylation, methylation, phosphorylation, and ubiquitination, with most of them occurring on the flexible unstructured tails that stick out of the nucleosome. Histone tail modifications commonly function by recruiting effector proteins or multimeric complexes to chromatin (**Fig. 1**), which subsequently alter nucleosomal structure to regulate DNA accessibility.[3] The exposed tail modifications are recognized by specialized protein domains, like bromodomains that bind acetyl marks.[4] However, there are examples where tail PTMs can also directly inhibit or enhance the formation of higher order chromatin structure, as observed by in vitro studies for H4K16ac and H4K20me3.[5,6] In these cases, tail PTMs regulate inter-nucleosomal interactions and they are thought to control the structure of large chromatin domains as opposed to having local effects at a single gene promoter or enhancer. During the last decade, PTMs have also been detected within the globular parts of the histone proteins.[7] These parts form the cylindrical structure of the histone octamer,[8] which is composed of the core (containing the histone-histone interfaces), the two circular sides, and the DNA entry-exit sites together with the DNA-bound face, also known as the lateral surface.

While the function of histone tail modifications as a dynamic recruiting platform is well documented,[4] the precise function of nucleosome lateral surface modifications remained poorly understood thus far. In fact, Cosgrove and colleagues predicted in 2004 that PTMs, which lie in the DNA-histone interface, could act by weakening this interaction[9] (**Fig. 1**). As a result, the disrupted histone-DNA

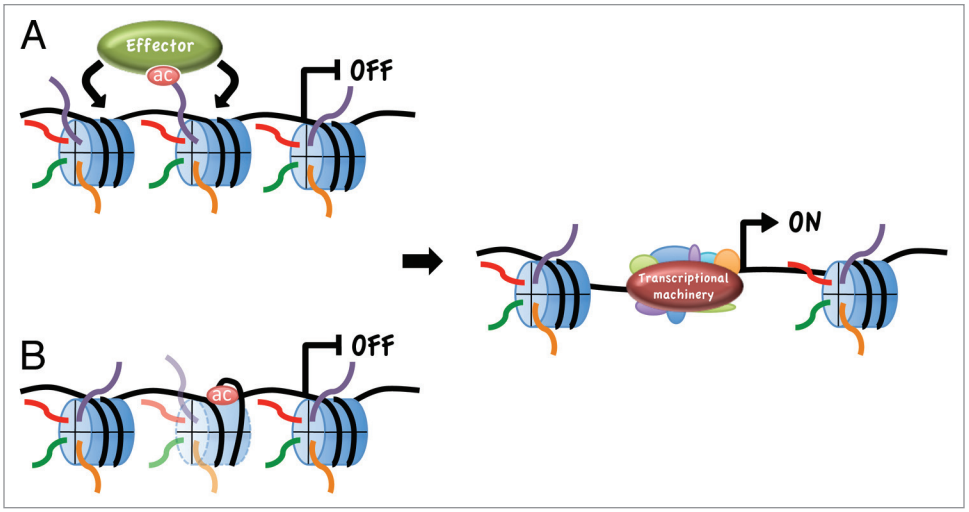

Figure 1. Mechanisms used by histone modifications located in the tail and lateral surface of the nucleosome. (**A**) Histone tail modifications (acetylation, red oval) commonly act as anchoring points for various effector proteins that can subsequently alter chromatin structure, enabling the transcriptional machinery to access the DNA. (**B**) Lateral surface modifications can change chromatin structure directly (without the need of an effector molecule) by weakening the DNA-histone interactions and destabilizing the nucleosome.

contacts may facilitate exchange of histone variants, nucleosome mobility or eviction. Hence, histone modifications on this lateral surface could have a direct impact on DNA accessibility and nucleosome dynamics in order to regulate processes like transcription. This model was supported at the time by in vitro experiments and studies in yeast, which showed that mutations of the modifiable residues around the dyad axis at the lateral surface, known as sin (SWI/SNF independent), alter nucleosomal stability and mobility.[10,11] The model was further developed recently by Fenley et al. (2010), who proposed that a decrease in the charge of the globular histone core by only one unit, for example by a single lysine acetylation, can lead to a substantial reduction of its interaction with the DNA.[12] On the contrary, a similar decrease in the charge of a histone tail will have no impact on nucleosomal stability.

A recent article by Tropberger et al. has now put flesh on this anticipated model by depicting the direct effect of a lateral histone modification (**Fig. 1**) on nucleosome dynamics.[1] Specifically, the authors studied acetylation on lysine 122 of histone H3 (H3K122ac), a modification located within the dyad axis of the nucleosome at a point where the DNA contacts the histone octamer with maximum affinity.[13] Several lines of evidence led the authors to define a role for this acetyl mark in transcriptional activation.[1] First, the authors locate H3K122ac (by immunofluorescence) exclusively within euchromatic regions in mouse embryonic fibroblasts. Second, they demonstrate that nucleosomes containing H3K122ac also possess other modifications and histone variants usually associated with active transcription, such as H3K9ac, H3K27ac, H3K4me3, acetylated H2A.Z and H3.3. Third, genome-wide distribution analysis by ChIP-sequencing shows that H3K122ac is enriched primarily at active gene promoters and enhancer elements. Notably, the levels of H3K122ac occupancy at these genomic loci are directly proportional to the levels of gene expression. Fourth, H3K122ac is induced upon stimulation of gene expression. Addition of estrogen in MCF7 cells induced estrogen receptor α (ERα)-mediated activation of the pS2 (*TFF1*) estrogen-responsive gene, coinciding with rapid deposition of H3K122ac and RNA Pol II loading. Fifth and most importantly, the authors established an elegant in vitro transcription assay to show that H3K122ac does not only correlate with transcriptional activation but functionally contributes to this process. H3K122 acetylation on its own was enough to stimulate transcription from a chromatin template while an equivalent tail acetylation at H3K18 could not. Consistent with the notion that individual tail acetylations are not sufficient for altering transcription, a previous study showed that only cumulative alterations in acetylated lysines within the H4 tail could affect gene expression.[14] Finally, mutation of K122 to arginine delayed activation of the *nmt1*$^{+}$ gene in *Schizosaccharomyces pombe*. Whether this delay in transcription is due to the absence of acetylation or merely to the presence of a different amino acid residue is unclear and of course, this remains a general challenge when using mutagenesis to study the effect of protein modifications in vivo.

The authors clearly demonstrated that H3K122ac directly stimulates transcriptional activation and then proceeded to identify the molecular mechanism underlying this effect. Since Tropberger and colleagues could not identify a binding protein for H3K122ac and the presence of this modification did not influence chromatin compaction, they considered histone eviction as a possible mechanism. Indeed, by using a histone eviction assay the authors demonstrated that nucleosomes containing this modification were more prone to displacement. This was consistent with previous studies, which showed that acetylations at the dyad axis, including H3K122ac, reduce histone-DNA interactions and promote nucleosome disassembly.[15,16] The

proposed nucleosome eviction mechanism is also supported by the enhanced binding of Pol II and the mediator subunit Med23, as a result of increased DNA accessibility, in genomic regions enriched with H3K122ac.[1] Also the presence of H3K122ac at transcriptional start sites (TSSs) correlates with decreased nucleosome occupancy,[1] in accordance with its function in nucleosome eviction. Another evidence that supports the nucleosome eviction mechanism is the co-existence of H3K122ac with the histone variants H3.3 and H2A.Z, which render the nucleosomes unstable and coincide with nucleosome-depleted regions at active promoters and enhancers.[17,18] Hence, the authors concluded that H3K122ac contributes to the overall instability of H3.3 and H2A.Z-containing nucleosomes in order to facilitate their displacement.

Previous studies linked nucleosome eviction to various histone chaperones,[19] as well as to chromatin remodelers like INO80,[20] Swi/Snf[21] and CHD1.[19] In their in vitro experiments, Tropberger and colleagues used the histone chaperone nucleosome assembly protein 1 (Nap1) to demonstrate the eviction of H3K122ac-containing nucleosomes. Although the factor(s) that mediates this displacement in vivo remains unknown,[1] there is strong evidence implicating Nap1 in this process. Earlier work has demonstrated that Nap1 together with p300, the enzyme that mediates H3K122ac, promote nucleosome eviction at the HTLV-1 promoter.[22] Another piece of evidence is the fact that Nap1 is a component of the p300 co-activator complex[23] and augments the activity of the p300 acetyltransferase.[24] Furthermore, other Nap1 family members form complexes with HATs in order to regulate their acetyltransferase activity.[25] Interestingly, Nap1 also cooperates with ATP-dependent remodelers (i.e., CHD1) to displace nucleosomes,[26,27] raising the possibility that such remodelers are involved in the H3K122ac eviction mechanism. Overall, Nap1 is a likely candidate for the H3K122ac-mediated eviction in vivo, but further work is required to elucidate completely this mechanism.

The authors identified p300 and its related CBP as the HATs that mediate H3K122 acetylation in vitro and within cells.[1] A lingering question, however, is how do these enzymes gain access to this residue while it is hidden beneath the DNA double helix? The importance of this question is exemplified by the fact that p300 acetylates H3K122 more efficiently in free histone octamers than in recombinant chromatin,[1] indicating that structural changes are required for the enzyme to reach its target. There are several scenarios that could explain how p300/CBP catalyze H3K122ac within native chromatin in vivo (**Fig. 2**). First, spontaneous unwrapping of the nucleosomal DNA could expose the buried lysine residue (**Fig. 2A**), thus providing access to p300 or CBP that would already be tethered to specific TSSs or enhancers by ERα.[28,29] Although, the rate of spontaneous unwrapping at the dyad axis might be slower than the high frequency of 4 times per second observed for the DNA entry and exit sites,[30] it could still be long enough for a successful encounter between p300 and H3K122. Second, other histone modifications present within the nucleosome could enable p300 to access H3 lysine 122 (**Fig. 2B**). For example, acetylation at H3K56,

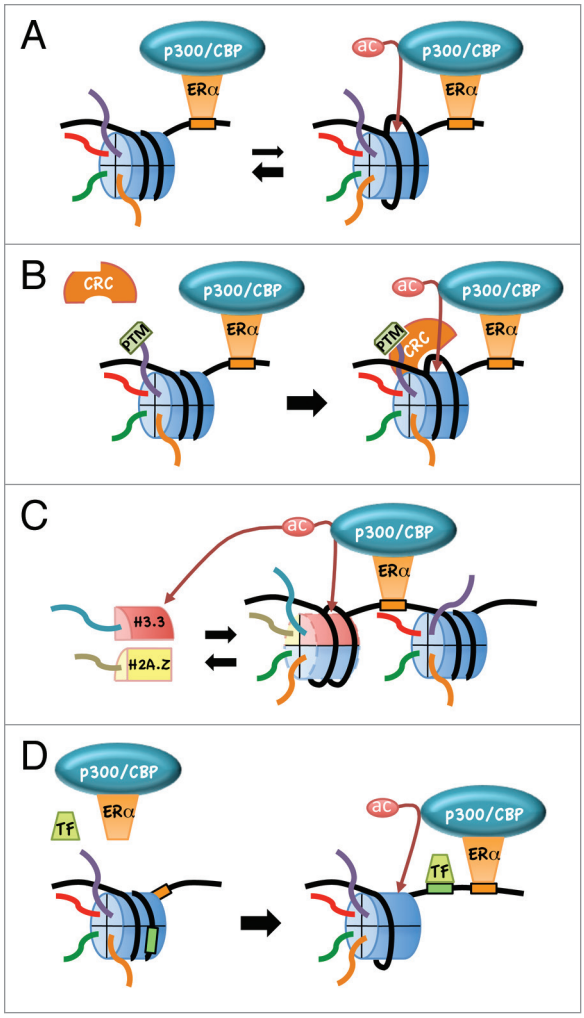

Figure 2. Potential scenarios of how HATs p300/CBP gain access to H3 lysine 122. (**A**) Spontaneous unwrapping of the nucleosome allows p300/CBP to access the previously hidden lysine. The HATs are already recruited at the relevant genomic regions, such as, at an estrogen-responsive element (orange box) through ERα. (**B**) A chromatin-remodeling complex (CRC), which is recruited by a histone tail modification (PTM), loosens the nucleosome and enables p300/CBP to access H3K122. (**C**) The instability and high histone turnover of H3.3/H2A.Z-containing nucleosomes provides accessibility of p300/CBP to K122. Alternatively, K122 is acetylated on H3.3 by p300/CBP just before incorporation into the nucleosome. (**D**) Cooperative binding of ERα with another transcription factor (TF) facilitates DNA unwrapping, allowing p300/CBP to reach H3K122.

which is detected in the same nucleosomes as H3K122ac,[1] could facilitate this process since it induces nucleosome accessibility by increasing the spontaneous DNA unwrapping rate by one order of magnitude.[31,32] Alternatively, a histone tail modification could recruit an ATP-remodeler that would open up the nucleosome prior to H3K122 acetylation. Many of the modifications that co-exist with H3K122ac, like H3K9ac, H3K18ac and H4K16ac,[1] could serve as recruiting signals for such a remodeler.[4] Of course, this scenario would require that these histone marks would be deposited immediately prior to H3K122ac. Interestingly, Tropbeger and colleagues already showed that maximum deposition of H3K9ac precedes H3K122ac at the pS2 promoter upon estrogen stimulation.[1] A third possible explanation is based on the fact that H3K122ac occurs in nucleosomes containing the histone variants H3.3 and H2A.Z. Nucleosomes containing these variants are less stable and more accessible than canonical nucleosomes.[17,33] Moreover, the H3.3/H2A.Z nucleosomes are associated with genomic regions of high histone turnover, and therefore, it remains possible that H3K122ac occurring at these sites, such as TSSs and active enhancers, is catalyzed immediately prior to histone incorporation (**Fig. 2C**). A final scenario could be based on the observation that cooperative binding and interactions of transcriptional activators at regulatory sites facilitates nucleosome invasion.[30,34] For instance, ERα-dependent recruitment of p300 at estrogen response elements could be accompanied with binding of additional transcription factors, such as retinoic acid receptor α (RARα),[35] that would aid p300 in gaining access to H3K122 (**Fig. 2D**). All the scenarios proposed above do not have to be mutually exclusive and therefore, modifying enzymes could be using a combination of these mechanisms to reach histone residues lying under the DNA on the lateral surface of the nucleosome.

Despite the extensive work performed by Tropberger and colleagues, some other fundamental questions relating to H3K122ac remain unexplored. Which histone deacetylase (HDAC) removes acetylation from this lysine? Treatment of cells with a general deacetylase inhibitor increased the levels of acetylation at lysine 122,[1] supporting the existence of an HDAC targeting H3K122ac. Considering that H3K122ac is dynamically regulated at the estrogen-responsive promoter *TFF1* during gene activation, identifying the implicated HDAC will provide a more precise explanation on how H3K122ac stimulates transcription. What is the function of H3K122ac at enhancer elements? The authors speculate that H3K122 acetylation regulates the expression of enhancer RNA (eRNA), since this modification facilitates binding of activators at transcribed regions, stimulates transcription in vitro and its enrichment at enhancers correlates with high levels of eRNA.[1] This speculation is further supported by a recent study which shows that estrogen-stimulated binding of ERα at enhancers in MCF7 cells causes a global increase in eRNA transcription.[36] These are the same conditions in which deposition of H3K122ac is induced by ERα[12] and thus, it now remains to be determined whether there is a link between H3K122ac and eRNA transcription. How do other modifications of lysine 122 relate to its acetylated form? It was previously shown that H3K122 is also methylated, formylated and succinylated.[37-39] Therefore, it will be interesting to know where the other K122 modifications are distributed in the genome and whether they are associated with transcription. For instance, it is possible that methylation of H3K122 is a repressive mark because it acts as a barrier against acetylation of the same residue, as it was proposed for H3K64.[40] What is the interplay of H3K122ac with other histone PTMs? Although, H3K122ac is sufficient on its own to stimulate transcription in vitro, in an in vivo situation this acetylation might collaborate with other histone PTMs to induce gene expression. There is an impressive overlap of H3K122ac with H3K27ac at enhancers and with H2A.Zac at TSSs,[1] raising the possibility of interdependence between H3K122ac and these modifications. Additionally, H3K122ac co-exists with H3K115ac on the same histone protein[41] suggesting that these two acetylations might be working together to destabilize the nucleosome.

Several recent findings indicate that other lateral surface modifications positioned at the dyad axis could function in a similar manner to H3K122ac[16,42] to induce transcription. For example, H3K115ac and H3T118ph that are nearby H3K122 reduce the free energy of the DNA-histone binding.[15,43] As a result, these modifications increase DNA accessibility and facilitate nucleosome mobility and disassembly mediated by chromatin remodeling factors. However, the contribution of these modifications toward nucleosome mobility might not be totally equivalent, as phosphorylation of T118 reduces the DNA-histone binding free energy more robustly than H3K122ac and H3K115ac. This notion is further supported by the fact that certain T118 mutations are lethal in yeast, while mutations in H3K122 have a slow growth phenotype.[44] Apart from affecting the DNA-histone contact, H3K122ac and the other dyad modifications could modulate the recognition of the octamer by histone chaperones and chromatin-remodelling factors. Considering that these regulators bind the octamer at sites that overlap with the designated path of the wrapped DNA,[45] it is conceivable that lateral modifications also control this interaction. Indeed, in vitro experiments with various modified histone peptides showed that H3K122ac, H3K115ac and H3T118ph regulate the affinity of chaperone NapS for H3.[45] In addition, it has been demonstrated that H3T118ph can alter the remodeling activity of SWI/SNF from nucleosome sliding to disassembly.[43] Moreover, phosphorylation of H3S47, another lateral surface modification that is nearby H3K122, regulates the interaction of histone chaperones with H3 variants in order to promote assembly of H3.3-containing nucleosomes. More specifically, H3S47ph stimulates the interaction of HIRA with H3.3 and reduces the association of CAF1 with H3.1.[46] Interestingly, a similar function has been defined for the DNA entry and exit site modification H3K56ac since it can change the remodeling specificity of SWR-C, resulting in promiscuous exchange of H2A or H2A.Z containing dimers.[47] In general, lateral surface modifications could influence the association of the histone octamer with any other molecules (i.e., DNA or proteins) to regulate chromatin dynamics.

A hypothesis arises from the work of Tropberger et al. that histone modifications occurring in different structural regions of the nucleosome employ distinct modes of action.[48] It is accepted that tail modifications typically function by recruiting effector molecules,[4] histone marks at the DNA entry-exit sites facilitate nucleosome unwrapping,[16] and now, other lateral surface modifications mediate nucleosome displacement by directly disrupting DNA-histone contacts.[1] Histone PTMs were also detected within the other two regions of the nucleosome:[49] the circular sides and the heart of the octamer containing the histone-histone interfaces. It is thought that modifications found on the outer surface of the circular sides would regulate inter-nucleosomal contacts[48] while modifications within the nucleosome core would affect octamer assembly. In fact, H4K91ac located in the center of the nucleosome weakens octamer stability by inhibiting the interaction between the H4/H3 tetramer and the H2A/H2B dimers.[50] We look forward to seeing whether the above distinct modes of action will hold true in the future, as more histone modifications are being discovered and functionally characterized. Lastly, more findings such as the ones reported by Tropberger and colleagues will prompt re-evaluation of the causal effects of histone modifications.[51,52]

Disclosure of Potential Conflicts of Interest

No potential conflict of interest was disclosed.

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