The HTLV-1 Tax protein: Revealing mechanisms of transcriptional activation through histone acetylation and nucleosome disassembly

Jennifer K. Nyborg *, Dinaida Egan, Neelam Sharma

Department of Biochemistry and Molecular Biology, Campus Box 1870, Colorado State University, Fort Collins, CO 80523-1870, USA

Abstract

The human T-cell leukemia virus, type-1 (HTLV-1)-encoded Tax protein is required for high-level transcription of the virus. Tax function is strictly dependent upon the phosphorylated form of the cellular transcription factor CREB (pCREB), and together they bind novel cAMP response elements located within the viral promoter. The DNA-bound Tax/pCREB complex recruits the cellular coactivators CBP/p300, which are essential for viral gene expression. The coactivators, via their histone acetyltransferase activity, function to promote changes in chromatin architecture that are permissive to transcriptional activation. Tax expression in vivo recruits p300 to the HTLV-1 promoter and correlates with depletion of nucleosomes from the integrated provirus. We recently developed a novel in vitro, chromatin-based experimental system that recapitulates the eviction of nucleosomes from the HTLV-1 promoter observed in vivo. These assays establish the essential function of Tax/pCREB recruitment of CBP/p300, and concomitant histone acetylation, in the nucleosome disassembly process. These observations are of particular significance, as Tax mediates disassembly of the full nucleosome octamer independent of transcriptional activity and ATP utilization. Instead, nucleosome eviction is absolutely dependent upon acetyl CoA and the histone chaperone Nap1. In this review, we will discuss HTLV-1, Tax transactivation, and our recent findings that uncover the critical role of Tax in promoting chromatin transitions that accompany activation of viral transcription. We will describe the phenomenon of acetylation-dependent promoter nucleosome disassembly and the emerging view that the formation of nucleosome-free promoter regions may represent a general prerequisite for transcriptional activation in eukaryotes.

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1. Introduction

In the nucleus of a eukaryotic cell, DNA is organized into a highly compacted structure called chromatin. Chromosomal DNA wraps around a protein octamer composed of the histone H2A/H2B dimer and the histone H3/H4 tetramer to form a nucleosome, the basic unit of chromatin [1,2]. Arrays of nucleosomes and other chromatin-associated proteins cooperate to compact and organize chromosomal DNA to fit into the nucleus, profoundly impacting genome accessibility and resulting in strong repression of gene expression. For example, the presence of a nucleosome near the start site of a gene physically hinders the binding of the large RNA polymerase-containing pre-initiation complex, resulting in transcriptional repression. To achieve highly regulated gene expression, the transcription machinery must utilize strategies that enable access to genes packaged into this dense chromatin environment. These molecular mechanisms are highly complex and poorly understood.

Retroviruses serve as outstanding model systems for the study of gene regulation in a chromatin context in higher eukaryotes. Following infection, the retroviral DNA genome stably and permanently integrates into a host-cell chromosome to form the provirus (Fig. 1). During this process, the proviral DNA is assembled into nucleosomal arrays that package and compact the viral genome such that the provirus is indistinguishable from a cellular gene and is regulated in an analogous manner. Because chromosomal integration is an obligatory event in the retroviral life cycle, these viruses have evolved highly efficient mechanisms to potently activate transcription (and thus viral replication) from compacted chromatin.

The human T-cell leukemia virus, type 1 (HTLV-1) is a clinically relevant retroviral model for both in vivo and in vitro studies on eukaryotic transcriptional activation in a chromatin context. Expression of the HTLV-1-encoded Tax protein is required for high-level transcription of the provirus [3–6]. As such, the Tax protein must have evolved a highly efficient mechanism to convert the provirus from a chromatin-dense, transcriptionally repressed state into an open, transcriptionally competent state. Recent studies have utilized in vivo and chromatin-based in vitro binding and transcription assays to significantly advance our understanding of Tax function in the
transition of the proviral promoter into a transcriptionally-competent state [7–16].

To achieve this transition, which is associated with subsequent high-level expression of the virus, Tax works in concert with the phosphorylated form of the cellular transcription factor CREB and the cellular histone acetyltransferases CBP/p300 (Fig. 1). Notably, we recently found that Tax recruitment of CBP/p300 promotes histone acetylation concomitant with reduced nucleosome density at the HTLV-1 promoter in vivo and in vitro [14,16]. These observations indicate that Tax is required for promoting histone acetylation and nucleosome eviction, supporting the emerging hypothesis that acetylation-dependent promoter nucleosome disassembly is a prerequisite for strong transcriptional activation.

In this review, we will discuss Tax activation of transcription from chromatin-assembled templates carrying the HTLV-1 promoter. This experimental system continues to serve as an outstanding tool for dissecting the molecular mechanisms of acetylation-dependent chromatin dynamics and the formation of transcriptionally-competent nucleosome-free regions. We will begin with a brief overview of HTLV-1-associated disease, viral replication, and viral infectivity. We will then describe the function of Tax as potent activator of HTLV-1 transcription, with specific emphasis on the role played by Tax in the orchestration of CBP/p300-mediated histone acetylation and the attendant chromatin dynamics that lead to nucleosome disassembly and transcriptional activation.

2. Clinical and molecular features of HTLV-1

HTLV-1 is a complex retrovirus that is the causative agent of multiple disparate diseases including a malignancy of T-lymphocytes called adult T-cell leukemia/lymphoma (ATLL) and a chronic inflammatory disease that is referred to as both tropical spastic paraparesis (TSP) and HTLV-1 associated myelopathy (HAM), commonly called TSP/HAM (for review, see [17]). The disease presents clinically with skin lesions (due to infiltrating leukemic cells), lytic bone lesions, and greater than 5% abnormal T-cells with large, multi-segmented nuclei. At the molecular level, ATLL is characterized by the presence of a chromosomally integrated HTLV-1 provirus present in aneuploid T-cells [21–24]. Expression of the HTLV-1 encoded Tax protein plays an essential role in the etiology of TSP/HAM, and is directly linked to malignant transformation [24].

The initial transmission of HTLV-1 to an uninfected individual occurs via cell–cell contact vertically, sexually, or through exposure to contaminated blood products. However, following infection, numerous lines of evidence implicate mitotic replication as the major route of viral expansion within the infected individual. Support for mitotic replication of the retrovirus includes (i) the near absence of extracellular virions, (ii) a high proportion of CD4+ T-cells carrying integrated provirus, (iii) low sequence variation of the provirus (e.g., viral replication via host cell DNA polymerase), and (iv) the ineffectiveness of reverse transcriptase inhibitors on reduction of proviral loads [25,26]. Together, these data support a dominant mechanism of proviral transmission in an infected individual via clonal expansion of T-cells carrying the provirus.

T-cell proliferation positively correlates with Tax expression, and individuals with the highest proviral load also express the highest levels of Tax [18,19,27]. As such, it is not surprising that in a small percentage of infected individuals, persistent proliferation of infected T-cells leads to the emergence of a dominant T-cell clone carrying the malignant phenotype [28]. Once transformed, however, the malignant ATLL cells acquire the ability to aggressively proliferate, often in the absence of Tax expression [29] (Fig. 2). Consistent with these observations, several studies have shown that in primary ATL leukemic cells and ATL cell lines the DNA within the 5′ LTR is hypermethylated, resulting in transcriptional silencing of the HTLV-1 provirus, and consequently the expression of Tax [30–32]. These studies support the hypothesis that Tax is required for the acquisition of genetic and epigenetic changes that occur during progression of the infected T-cell to the leukemic state. However, once transformation is
achieved, Tax expression is irrelevant to the maintenance of the malignant state. These studies lend strong support to the hypothesis that the cell-proliferative properties of Tax are interwoven with the oncogenic properties of the virus. A schematic showing many of the pleiotropic properties of Tax is shown in Fig. 3.

3. The HTLV-1 promoter

Three highly conserved 21 bp enhancer elements, located upstream of the RNA initiation site, are essential for Tax-activated transcription [3–5,33]. These sequences, referred to as viral cAMP response elements (vCREs), carry a core off-consensus CRE that is immediately flanked by short stretches of GC-rich DNA. Together, the vCREs comprise the Tax-responsive enhancer elements of the HTLV-1 promoter. The octanucleotide core CRE is the binding site for the cellular transcription factor CREB (as well as other ATF/CREB family members) [34–40]. Tax binding to the vCREs requires protein–protein interaction with DNA-bound CREB [41] and protein–DNA contact within the minor groove of the adjacent GC-rich sequences [42–45] (Fig. 1). The promoter-bound Tax/CREB complex is absolutely required for transcription of the proviral genome.

4. CREB phosphorylation is required for Tax function

The ubiquitously expressed cellular transcription factor CREB is one of the most widely studied prototypic signal-dependent transcription factors in higher eukaryotes. The basic leucine zipper region of CREB binds to CREs and regulates the expression of a significant percentage of genes in the human genome [46–48]. The transcriptional activity of CREB is regulated by phosphorylation at serine 133 (pCREB), with over 300 distinct extracellular stimuli converging on numerous kinases that phosphorylate CREB at this site (for review, see [49]). According to the established paradigm, pCREB is absolutely required to recruit the cellular coactivators CBP/p300 to target promoters and activate transcription [50–53]. The transducers of regulated CREB (TORC) proteins have recently been identified as additional CREB coactivators that facilitate activation of CREB target genes [54–59]. Underscoring the significance of the physical and

![Fig. 2. Model illustrating the hypothetical sequence of events in the proliferation and transformation of HTLV-1-infected T-cells. Figure loosely adapted from Matsuoka and Jeang [24].](image)

![Fig. 3. Pathways of Tax dysregulation in an HTLV-1-infected cell. Various Tax-deregulated genes and Tax-interacting proteins are shown. A more thorough discussion of the impact of Tax on cellular transcription factors, chromatin modifying enzymes, signaling pathways, and cell cycle regulation is provided in an excellent recent review (see [116]).](image)
functional relationship between Tax and CREB, the TORC proteins have also been shown to physically interact with Tax and enhance HTLV-1 transcription [58,59]. These studies suggest that interactions between Tax, pCREB, and TORC proteins cooperate in the strong activation of HTLV-1 transcription.

Although CREB (or a CREB family member) is required for Tax binding to the HTLV-1 promoter, the functional consequence of CREB phosphorylation in Tax transactivation has been controversial. Several in vivo studies show that protein kinase A phosphorylation of CREB significantly enhances Tax transactivation, while other studies show that CREB phosphorylation is not necessary for optimal Tax transactivation [60–62]. We recently addressed this controversy using in vitro approaches and found that pCREB, but not CREB, significantly enhances the stability of the quaternary complex formed with Tax, the KIX domain of CBP/p300 (see below), and the vCRE [63,64]. We also demonstrated that Tax, in complex with pCREB (but not CREB), was required to recruit full-length CBP or p300 to the HTLV-1 promoter and activate viral transcription [15]. Surprisingly, pCREB alone (in the absence of Tax) was defective for CBP/p300 recruitment and transcriptional activation, while the addition of Tax dramatically transformed the pCREB/DNA complex into a high-affinity binding site for full-length CBP/p300. Together, these data demonstrate that Tax, in complex with pCREB, is essential for recruitment of CBP/p300 to the HTLV-1 promoter and the activation of transcription.

5. Tax induces CREB phosphorylation

Based on the essential role for pCREB in Tax transactivation, it is likely that the virus evolved a mechanism to promote CREB phosphorylation and ensure high-level viral gene expression. Using a panel of uninfected and HTLV-1-infected human T-cell lines, we recently detected constitutively elevated pCREB levels only in the Infected cells, and enhanced Ser133 CREB phosphorylation following its identification as a transcriptional coactivator for CREB, both CBP and p300 are recruited by a large number of promoter-bound cellular and viral transcription factors (Fig. 4). At least four domains (C/H1, KIX, C/H3, and CR2) are known to participate in protein–protein interactions with transcription factors [69]. Of these, the KIX domain is the primary site of protein–protein interaction with vCRE-bound Tax/pCREB [9, 15, 64, 70–73]. Interestingly, we recently found that Tax and pCREB simultaneously and independently bind two distinct sites on the surface of KIX, which together contribute to the synergy of Tax and pCREB in CBP/p300 recruitment [64].

Importantly, several studies have demonstrated that the Tax/pCREB complex recruit full-length CBP/p300 to the HTLV-1 promoter in vivo and in vitro [8,9,11,14–16,74]. For example, a study from our laboratory using chromatin immunoprecipitation (ChIP) assays demonstrated that Tax expression correlates with a dramatic increase in p300 binding at the chromosomally-integrated HTLV-1 promoter, concomitant with strong transcriptional activation [Fig. 5] [14]. These studies support the biological relevance of the interaction between Tax and CBP/p300 in mediating regulated expression of the virus.

6. The cellular coactivators CBP/p300

CBP/p300 are very large (~300 kD) structurally and functionally homologous coactivator proteins that are central mediators of gene expression in Metazoa [67,68]. These proteins do not directly bind DNA, but are recruited to promoters by DNA-bound transcription factors. Although CBP (CREB binding protein) was originally named following its identification as a transcriptional coactivator for CREB, both CBP and p300 are recruited by a large number of promoter-bound cellular and viral transcription factors (Fig. 4). At least four domains (C/H1, KIX, C/H3, and CR2) are known to participate in protein–protein interactions with transcription factors [69]. Of these, the KIX domain is the primary site of protein–protein interaction with vCRE-bound Tax/pCREB [9, 15, 64, 70–73]. Interestingly, we recently found that Tax and pCREB simultaneously and independently bind two distinct sites on the surface of KIX, which together contribute to the synergy of Tax and pCREB in CBP/p300 recruitment [64].

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7. Histone acetylation and gene expression

CBP/p300 each carry intrinsic histone acetyltransferase (HAT) activity, and this activity appears to be the prominent means by which the coactivators regulate gene expression [75,76]. Transcription factor recruitment of CBP/p300 to target promoters and enhancers correlates with acetylation of the histone H3 and H4 tails [67,75–80]. Histone acetylation has emerged as a defining event in the control of gene expression and is the best-characterized post-translational modification associated with gene activation [81,82]. The association of CBP/p300 at specific genetic loci is increasingly recognized as a hallmark of transcriptionally active genes [83,84].

Although the precise mechanism by which acetylation promotes transcription is not fully understood, histone tail acetylation...
unequivocally alters the physical properties of chromatin. Lysine charge neutralization, achieved through histone tail acetylation, reduces internucleosomal interactions and results in unfolding of the chromatin fiber [85]. Once unfolded, acetylation weakens the histone tail–DNA interactions, but has no effect on the overall stability of the nucleosome [86–89]. The question of whether unfolding of the chromatin fiber is sufficient for gene activation or whether additional chromatin transitions are required remains at the forefront of research on epigenetic regulation of eukaryotic gene expression.

8. Histone modifications at the HTLV-1 promoter in vivo

Several histone post-translational modifications have been shown to strongly influence gene expression [90]. Most modifications occur on the histone amino-terminal tails and influence either gene activation or gene repression. Specifically, histone H3 methylation and H3/H4 acetylation have been correlated with Tax-dependent regulation of HTLV-1 transcription [8,10,11,14,74,91,92]. The histone methyltransferases CARM1 and SUV39H1 have opposing effects on HTLV-1 transcription, depending upon the site within the histone tail targeted by each enzyme [91,92]. Conversely, the histone acetyltransferases CBP/p300 have been consistently associated with HTLV-1 transcriptional activation [8–11,14,16,74].

Chromatin immunoprecipitation (ChIP) assays have demonstrated a correlation between CBP/p300 binding to the HTLV-1 promoter and histone acetylation within the provirus [8,10,11,14,74] (Fig. 5). These studies provide strong, albeit indirect, support for the hypothesis that CBP/p300 recruitment serves to promote local histone acetylation, altered chromatin architecture, and gene activation. Interestingly, two previously published papers found that Tax interacts with multiple HAT-containing coactivators, including the CBP/p300-associated factor (PCAF), which raises the question as to which HAT is necessary for Tax transactivation in vivo [93,94]. In one study, the HAT activity of PCAF was found to be integral to transcriptional activation [93], whereas the other study found that the HAT activity was dispensable [94]. While both of these studies show a direct interaction between Tax and PCAF, we have been unable to detect the association of PCAF with the HTLV-1 promoter by extensive ChIP analysis in vivo and using a purified system in vitro ([16,74] and unpublished data). Therefore, the functional relevance of PCAF in Tax transactivation remains controversial.

Dynamic regulation of genes requires the recruitment of HAT proteins as well as the enzymes that participate in the removal of acetyl groups from the promoter–associated histones. The histone deacetylase complexes (HDACs) carry out this function, and thus are the counterbalance to CBP/p300-mediated activation of gene expression. Several studies have established that Tax and HDACs physically interact in vivo and in vitro, and that HDAC binding to the HTLV-1 promoter strongly represses transcription [10,11,74–95]. Two studies directly examined the interplay between Tax and HDAC binding in vivo and demonstrated mutual exclusivity at the proviral promoter through direct competition [10,11]. Ectopic overexpression of Tax or CBP alleviated the repressive effects of the HDACs, illustrating the critical balance between histone acetylation and deacetylation in the regulation of HTLV-1 transcription [10,11,95].

9. In vitro chromatin-based system for studies of Tax function

The in vivo studies summarized above establish that Tax recruitment of CBP/p300 correlates with histone acetylation and strong HTLV-1 transcriptional activation. Dissection of the molecular steps that facilitate transactivation, however, require a biochemically-defined in vitro approach. One long-standing challenge in pursuing mechanisms of gene activation in vitro has been the availability of a suitable experimental system that resembles a physiological context. This challenge has been largely overcome with the development of chromatin-based assays that enable assembly of evenly spaced nucleosomes onto a promoter template to study coactivator function, histone modifications, and concomitant transcriptional activation from a repressed chromatin context [96–98]. Several laboratories have adapted this experimental system to incorporate nucleosomes
into the HTLV-1 promoter for molecular characterization of Tax-mediated factor binding, histone modification, and transcription initiation [7-10,13,15,16,99].

The HTLV-1-based chromatin systems utilize DNA templates (purified fragments or plasmids) that carry the full Tax-responsive HTLV-1 promoter (or reiterated copies of the vCREs) assembled with purified native or recombinant histones to form nucleosomal arrays. The chromatin-assembled viral promoter is assayed in the presence of various highly purified, recombinant transcription factors (Tax, pCREB), coactivators (CBP, p300), cofactors (Ac-CoA), and/or nuclear extracts. This experimental system is fundamental to the study of CBP/p300, as it provides the essential substrates for their intrinsic HAT activity, an enzymatic activity inextricably linked to the function CBP/p300, as it provides the essential substrates for their intrinsic pCREB), coactivators (CBP, p300), cofactors (Ac-CoA), and/or nuclear extracts. This experimental system is fundamental to the study of CBP/p300, as it provides the essential substrates for their intrinsic HAT activity, an enzymatic activity inextricably linked to the function of the coactivators. Importantly, the addition of purified Tax to the chromatin templates in the presence of nuclear extract recapitulates the strong Tax transactivation observed in vivo (>100-fold) [7-9,13,15]. In contrast, nucleosome-free (e.g., naked) templates are only modestly responsive to the addition of Tax, demonstrating that the presence of chromatin facilitates Tax function and further validates the physiological relevance of this system [7].

10. Tax transactivation in a chromatin context in vitro

The value of this experimental system resides in its use of natural activators and coactivators, its ability to recapitulate in vivo Tax transactivation, and its adaptability to biochemical dissection. The use of this chromatin-based system has significantly enhanced our understanding of Tax transactivation function, and the role of chromatin in gene activation. The salient conclusions that have emerged from these studies are summarized here:

1. Strong activation of HTLV-1 transcription in a chromatin context is absolutely dependent upon the addition of purified Tax and pCREB; their absence results in transcription that is often below the level of detection.
2. Tax and pCREB bind to the chromatin-assembled vCREs and both are required to strongly recruit native or purified CBP/p300 [8,9,13,15,16].
3. Recruitment of full-length CBP/p300 occurs via protein–protein interaction between both Tax and pCREB with the KIX domain of the coactivators [9,15]. This is an essential step, as inhibition of recruitment attenuates Tax transactivation [9].
4. The intrinsic HAT activity of the coactivators is essential to Tax transactivation, demonstrated by a strict Ac-CoA dependence and significantly reduced HTLV-1 transcription using either a p300 HAT mutant or LysCoA, a selective inhibitor of CBP/p300 HAT activity [7-9].
5. Deletion of the amino-terminal histone tails significantly reduces dependence on Ac-CoA but does not block Tax transactivation, suggesting that histone acetylation and amino-terminal tail deletion are functionally equivalent [7]. Direct evidence for histone acetylation has been verified by the detection of acetylated nucleosomes on the HTLV-1 promoter template [7-9].

Together, these data provide a clear link between Tax/pCREB recruitment of CBP/p300, Ac-CoA utilization, histone acetylation, and transcriptional activation. This work establishes that a fundamental function of Tax is the orchestration of coactivator binding, histone acetylation, and the promotion of the chromatin architectural changes permissive to transcriptional activation.

11. Tax mediates acetylation-dependent nucleosome disassembly

In a recently published study, we made the unexpected observation that p300 recruitment to a chromosomally-integrated HTLV-1 promoter correlates with a decrease in acetylated histones [14]. This reduction in histone acetylation coincided with a similar reduction in histone H3 and linker histone H1 levels, indicating that the observed decrease in histone acetylation levels actually reflected reduced nucleosome density at the HTLV-1 promoter. These data suggested that Tax induces nucleosome clearance at the promoter to enable pre-initiation complex formation and strong transcriptional activation. Interestingly, a report from the Laybourn laboratory showed a reduction in global histone levels in HTLV-1-infected T-cell lines, and these changes required Tax expression [100]. The long-term biological consequence of reduced global histone levels in HTLV-1-infected cells is unknown, but may promote genome instability associated with malignant transformation.

To explore the molecular basis for the observed reduction in nucleosomes specifically at the HTLV-1 promoter, we modified our in vitro-based assay to incorporate an immobilized chromatin-assembled HTLV-1 promoter fragment. This enabled visualization of promoter nucleosomes during the course of the reactions. Remarkably, we also observed a significant reduction in nucleosome occupancy on the immobilized promoter template that is dependent on Tax/pCREB binding, CBP/p300 recruitment, and Ac-CoA [16]. Nucleosome eviction is uncoupled from transcription, indicating that the process is not a consequence of transcriptional initiation or elongation. Nucleosome eviction is independent of ATP, indicating that chromatin remodeling complexes do not participate in the reaction. This last observation is consistent with previous studies demonstrating Brg1/Brm-independent Tax transactivation in vivo [12,14].

A critically important detail that emerged from the in vitro nucleosome eviction studies was a strict prerequisite for CBP/p300 histone acetylation in nucleosome disassembly [16]. As observed in the in vitro transcription assays described above, the addition of inhibitors of the CBP/p300 HAT activity also blocks the clearance of nucleosomes from the promoter. This finding is consistent with the requirement for recruitment of the coactivators and the addition of Ac-CoA. We found that the histone amino-terminal tails served as the target of coactivator-mediated acetylation. These data indicate that histone tail acetylation is sufficient for disassembly of the nucleosome octamer.

12. The histone chaperone Nap1 facilitates acetylation-dependent nucleosome disassembly

While these data clearly implicate Tax, pCREB, and CBP/p300 in the overall process of nucleosome disassembly, we found that the histone chaperone Nap1 also plays a direct role in octamer removal. Nap1 was initially introduced into the reaction as a component of the chromatin assembly reaction, as Nap1 generates regularly spaced nucleosomes during assembly [96]. Nap1 was originally identified as a histone binding protein based on its ability to bind all four core histones in vitro (see [101] for review). However, emerging evidence has identified a prominent role for histone chaperones in maintaining the critical balance between chromatin assembly and disassembly [102]. Nap1 has been implicated in H2A/H2B dimer removal and exchange as a mechanism to regulate DNA accessibility and to maintain chromatin integrity and fluidity [103-107]. Nap1 has also been shown to bind CBP/p300 at the C/H3 domain (Fig. 4), and displace the H2A/H2B dimer from nucleosomes following p300 acetylation [108–110]. To our knowledge, however, our studies reveal the first example of Nap1 functioning in acetylation-dependent eviction of the full histone octamer [16].

13. Discussion and conclusions

Together, the data presented above support an emerging mechanism for negotiating chromatin to activate transcription via acetylation-dependent disassembly of promoter-associated nucleosomes. Specifically at the HTLV-1 promoter, the published data
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References


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H. Reinke, W. Horz, Histones are first hyperacetylated and then lose contact with the activated PHOS promoter, Mol. Cell 11 (2003) 1599–1607.

