

What's Up and Down with Histone Deacetylation and Transcription?

Michael J. Pazin and James T. Kadonaga*

Department of Biology
and Center for Molecular Genetics
University of California, San Diego
La Jolla, California 92093-0347

Chromatin structure is an important component of gene expression, and recent developments have led to increased interest in the role of core histone acetylation in transcriptional regulation (for reviews, see Roth and Allis, 1996; Wade and Wolffe, 1997; Grunstein, 1997). It has been recognized for many years that there is a general correlation between core histone acetylation and gene activity, and the notion that core histone acetylation facilitates gene expression has gained further support as transcription factors such as Gcn5, CBP/p300, and TAF_{II}250 have been found to possess histone acetyltransferase activity.

Conversely, it has been thought that core histone deacetylation leads to transcriptional repression. This

Minireview

RbAp48 (RbAp46 and RbAp48 are closely related proteins). Perhaps significantly, RbAp48 is associated with HDAC1 (Taunton et al., 1996) and is also a subunit of chromatin assembly factor 1 (for reviews, see Roth and Allis, 1996; Grunstein, 1997). A brief guide to the factors that were studied in each of the papers is given in Table 1.

What do these seven papers say? Do they have a common message? The major point of these papers is that transcriptional repression by a sequence-specific DNA-binding factor can be mediated by the recruitment of a deacetylase (Rpd3/HDAC1/HDAC2) to the promoter region. More specifically, each of the papers proposes a chromatin-specific mechanism for repression by a sequence-specific DNA-binding protein that involves deacetylation of core histones by a histone deacetylase that is linked to the DNA-bound repressor via Sin3 and/

Table 1. A Quick Guide to the Papers and Proteins

Paper	Mad/Mxi Proteins	Nuclear Receptors	Ume6	Sin3 Proteins	N-CoR SMRT	Rpd3		SAP18 SAP30
						HDAC1	HDAC2	
Laherty et al. (1997)	X			X		X		
Hassig et al. (1997)	X			X		X	X	
Zhang et al. (1997)	X			X		X	X	X
Kadosh and Struhl (1997)			X	X		X		
Nagy et al. (1997)		X		X	X	X		
Heinzel et al. (1997)	X	X		X	X	X		
Alland et al. (1997)	X			X	X	X		

or N-CoR/SMRT (Figure 1). Because HDAC1 as well as a yeast Rpd3-containing complex can deacetylate core histones (or a histone H4 peptide) in vitro (Rundlett et al., 1996; Taunton et al., 1996), it was postulated that transcriptional repression involves core histone deacetylation, but whether or not localized histone deacetylation occurs at the repressed target genes remains to be tested. In addition, a biochemical interaction (of either a direct or an indirect nature) between Sin3 and Rpd3/HDAC1/HDAC2, as shown in the new papers, is nicely in accord with the findings of genetic studies of Sin3 (= Rpd1) and Rpd3 (= Sdi2), which have suggested that the two factors function in the same regulatory pathway (Vidal and Gaber, 1991; Stillman et al., 1994).

Some, but not all, transcriptional repressors appear to function via Sin3 and deacetylases. For example, Tup1, Acr1, and ERF2 do not require Rpd3 or HDAC2 to mediate transcriptional repression (Heinzel et al., 1997; Kadosh and Struhl, 1997). The results further indicated that the histone deacetylases may not be fully responsible for repression by the corepressors, Sin3 and/or N-CoR. For instance, Laherty et al. (1997) found that deletion of the HDAC interaction domain of mSin3A did not eliminate the ability of mSin3A to mediate transcriptional repression. Thus, mSin3A also appears to be able to repress transcription by an HDAC-independent mechanism. In addition, there are specific regions of N-CoR that are important for transcriptional repression that are distinct from the sites that interact with mSin3 proteins, which suggests that N-CoR can repress transcription by Sin3-dependent and Sin3-independent mechanisms (Heinzel et al., 1997). Alland et al. (1997) have also identified a splice variant of mSin3B that interacts with N-CoR but not with HDAC1, yet is still able to repress transcription. It therefore appears that a portion of the transcriptional repression by some repressors occurs via protein deacetylation.

All of the new papers involve transcriptional repression by the Sin3 corepressor and Rpd3/HDAC1/HDAC2 deacetylases (Table 1). Examination of the *Saccharomyces cerevisiae* DNA sequence database suggests that yeast does not possess a protein related to N-CoR or SMRT. It is thus possible that there is a core repression mechanism conserved from yeast to humans involving Sin3 and Rpd3, and that N-CoR and SMRT are corepressors that have later evolved to allow factors, such as the unliganded nuclear receptors and Mad/Mxi proteins, to mediate transcriptional repression via the Sin3-Rpd3 pathway.

Does Core Histone Deacetylation Lead to Transcriptional Repression?

Thus far, it has been generally thought that the deacetylation of core histones by HDACs leads to transcriptional repression. This hypothesis is quite reasonable given the overall correlation between histone acetylation and transcriptional activity. Moreover, a yeast Rpd3-containing complex and recombinant HDAC1 can deacetylate core histones (or a histone H4 N-terminal peptide) in vitro (Rundlett et al., 1996; Taunton et al., 1996), and deletion of either the *RPD3* gene or the *HDA1* gene (which encodes a protein that is related to Rpd3) in yeast leads to increased levels of core histone acetylation in vivo (Rundlett et al., 1996). It therefore seems likely that acetylated core histones are a physiological substrate for Rpd3 and related proteins, but it remains to be determined whether deacetylation of core histones does indeed mediate transcriptional repression by these factors.

A simple model in which core histone acetylation leads to gene activation predicts that global hyperacetylation of chromatin would lead to widespread transcriptional activation. In yeast *rpd3* deletion strains, however, a defect in both transcriptional repression as well as transcriptional activation is observed (see, for example, Vidal and Gaber, 1991; Rundlett et al., 1996). Specifically, there is a 2- to 5-fold derepression of uninduced genes and a 2- to 5-fold reduction in the levels of expression of activated genes (Vidal and Gaber, 1991). In addition, Van Lint et al. (1996) performed a differential display analysis of cells treated with the histone deacetylase inhibitor, trichostatin A. In that study, the deacetylase inhibitor induced a change (i.e., either an increase or a decrease) in the transcriptional activity of only 8 out of the approximately 340 genes that were examined, even though the inhibitor did increase the overall level of core histone acetylation. (Van Lint et al. [1996] also observed induction of HIV-1 transcription and repression of *c-myc* transcription upon treatment with either of the deacetylase inhibitors, trichostatin A or trapoxin. The *c-myc* repression was rapid, as transcripts were no longer detectable 2 hr after treatment, and hence, it is difficult to ascribe this repression to the transcriptional induction of a gene that encodes a *c-myc* repressor.) Therefore, the available data indicate that a global increase in core histone acetylation does not induce widespread transcription.

Studies of position-effect variegation and telomeric silencing, which are forms of localized transcriptional repression that occur in the vicinity of heterochromatin,

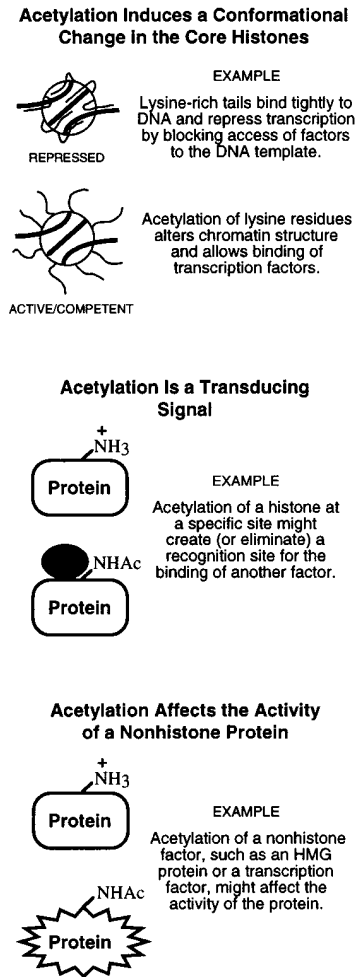


Figure 2. Some Hypothetical Mechanisms by which Protein Acetylation Could Affect Transcriptional Activity
These models are not mutually exclusive and are not necessarily nonoverlapping.

have also led to unexpected findings with regard to core histone acetylation and gene expression. In particular, *rpd3* deletion strains in yeast (which possess increased levels of histone acetylation) exhibit decreased transcriptional activity near telomeres relative to their wild-type counterparts (De Rubertis et al., 1996; Rundlett et al., 1996). In addition, enhancement of position-effect variegation (i.e., a decrease in transcriptional activity near heterochromatin) was seen in *Drosophila rpd3* mutant strains (De Rubertis et al., 1996). Thus, in these instances, an increase in histone acetylation correlated with a decrease in transcriptional activity. These and other findings collectively suggest that the relation between Rpd3/HDAC function and transcriptional activity may be more complex than a matter of histone deacetylation and consequent transcriptional repression.

How Might Protein Acetylation Regulate Transcription?

A few hypothetical models for the regulation of transcriptional activity by protein acetylation are depicted in Figure 2. These models are not mutually exclusive and may partially overlap.

In the first (upper) model, modification of charged lysine residues in the histone tails by acetylation increases the access of transcription factors to the DNA template. While there is not a perfect correlation between acetylation and transcriptional activity, it is possible that the changes in core histone structure that occur upon acetylation may facilitate transcription but not be sufficient to induce transcription of an inactive gene. In fact, core histone acetylation could be involved at the level of transcriptional competence (i.e., the facility by which a gene can be transcribed) rather than transcriptional induction. For example, analysis of both coding and noncoding regions of the chicken β -globin locus revealed a 33 kbp region of core histone hyperacetylation, which comprises transcriptionally active and inactive β -globin genes, that corresponds closely with a DNase I general sensitivity domain (Hebbes et al., 1994). In such instances, core histone acetylation may contribute to the establishment and/or maintenance of a transcriptionally competent state in which the chromatin is in an altered ("open") conformation.

In the second (middle) model, the specific acetylation of a lysine residue (of a histone or nonhistone protein) creates (or eliminates) a signal that is recognized by another factor. This model is suggested, for example, by the distinct acetylation patterns of conserved lysine residues in histone H4 of *Drosophila* (Turner et al., 1992). In *Drosophila* polytene chromosomes, H4 acetylated at positions 5 or 8 is distributed throughout euchromatin, H4 acetylated at position 12 is preferentially associated with β -heterochromatin, and H4 acetylated at position 16 is preferentially associated with the hyperactive male X chromosome. This specificity in the localization of differently acetylated forms of H4 suggests that acetylated H4 is acting as a signal. (In addition, the localization of H4 acetylated at lysine 12 in *Drosophila* β -heterochromatin indicates, once again, that histone acetylation does not necessarily correlate with gene activity.) It would be interesting to investigate the consequences of acetylation at specific sites in histones. For instance, downstream effector molecules, such as co-activator or corepressor complexes, might bind to H4 that is acetylated at specific positions (see, for instance, Edmondson et al., 1996).

The third (bottom) model postulates that acetylation of nonhistone proteins is important for transcriptional regulation. For example, high mobility group (HMG) proteins are acetylated at lysine residues, and the deacetylation of HMG proteins is inhibited by sodium butyrate (a reagent that is commonly used to inhibit histone deacetylation). Therefore, HMG protein deacetylation may contribute to the transcriptional effects that are seen with Rpd3 and related proteins. In addition, other proteins, such as transcription factors and components of the basal transcription machinery, could possibly be modified by acetylation.

The specificity of protein acetylation is reminiscent of that of protein phosphorylation. Some phosphorylation events induce a conformational changes in proteins that alter their functions. Other phosphorylation sites serve as docking sites for effector molecules. Further studies will reveal the extent of such parallels between protein acetylation and protein phosphorylation.

***Are the Deacetylases Involved
in Transcriptional Activation?***

While there has been considerable effort devoted to the study of deacetylases as transcriptional repressors, is it possible that they also function as transcriptional activators? For example, the yeast Rpd3 protein is required for full activation as well as for full repression of gene expression (Vidal and Gaber, 1991; Rundlett et al., 1996). In addition, a transcriptional activation function of Rpd3 is consistent with the reduced transcriptional activity that is observed upon the loss of Rpd3 function in *Drosophila* or yeast (De Rubertis et al., 1996; Rundlett et al., 1996). Alternatively, these data could be interpreted to indicate that loss of Rpd3 leads to repression of a transcriptional activator (and hence, a reduction in gene activity), and such an indirect effect for activation by Sin3 has been proposed.

The recent studies of the effects of histone deacetylases upon transcription have generally characterized the deacetylases as Gal4 or LexA fusions with synthetic reporter genes containing multiple (typically, four or five) Gal4- or LexA-binding sites upstream of the core promoter. It is therefore possible that these assays did not detect an activation function for the deacetylases. If histone deacetylases were components of large protein complexes that regulate transcription, it seems plausible that such complexes could possess the capacity to activate or to repress transcription. In this regard, it is interesting to note that many of the sequence-specific DNA-binding factors that function via the Sin3 and Rpd3/

- Edmondson, D.G., Smith, M.M., and Roth, S.Y. (1996). *Genes Dev.* 10, 1247-1259.
- Grunstein, M. (1997). *Nature*, in press.
- Hassig, C.A., Fleischer, T.C., Billin, A.N., Schreiber, S.L., and Ayer, D.E. (1997). *Cell*, this issue.
- Hebbes, T.R., Clayton, A.L., Thorne, A.W., and Crane-Robinson, C. (1994). *EMBO J.* 13, 1823-1830.
- Heinzel, T., Lavinsky, R.M., Mullen, T.-M., Söderström, M., Laherty, C.D., Torchia, J., Yang, W.-M., Brard, G., Ngo, S.G., Davie, J.R., et al. (1997). *Nature* 387, 43-48.
- Kadosh, D., and Struhl, K. (1997). *Cell*, this issue.
- Laherty, C.D., Yang, W.-M., Sun, J.-M., Davie, J.R., Seto, E., and Eisenman, R.N. (1997). *Cell*, this issue.
- Nagy, L., Kao, H.-Y., Chakravarti, D., Lin, R., Hassig, C.A., Ayer, D.E., Schreiber, S.L., and Evans, R.M. (1997). *Cell*, this issue.
- Roth, S.Y., and Allis, C.D. (1996). *Cell* 87, 5-8.
- Rundlett, S.E., Carmen, A.A., Kobayashi, R., Bavykin, S., Turner, B.M., and Grunstein, M. (1996). *Proc. Natl. Acad. Sci. USA* 93, 14503-14508.
- Stillman, D.J., Dorland, S., and Yu, Y. (1994). *Genetics* 136, 781-788.
- Taunton, J., Hassig, C.A., and Schreiber, S.L. (1996). *Science* 272, 408-411.
- Turner, B.M., Birley, A.J., and Lavender, J. (1992). *Cell* 69, 375-384.
- Van Lint, C., Emiliani, S., and Verdin, E. (1996). *Gene Expression* 5, 245-253.
- Vidal, M., and Gaber, R.F. (1991). *Mol. Cell. Biol.* 11, 6317-6327.
- Wade, P.A., and Wolffe, A.P. (1997). *Current Biol.* 7, R82-R84.
- Yang, W.-M., Inouye, C., Zeng, Y., Bearss, D. and Seto, E. (1996). *Proc. Natl. Acad. Sci. USA* 93, 12845-12850.
- Zhang, Y., Iratni, R., Erdjument-Bromage, H., Tempst, P., and Reinberg, D. (1997). *Cell*, this issue.