Chromatin: **Histone acetyltransferases in control**

Paul A. Wade and Alan P. Wolffe

Several transcriptional regulators have been found to act as enzymes that acetylate histones. The targeted post-translational modification of histones within regulatory nucleoprotein complexes provides an attractive mechanism for controlling transcription within a chromatin environment.

Address: Laboratory of Molecular Embryology NICHHD, NIH, Building 18T, Room 106, Bethesda, Maryland 20892–5431, USA.
E-mail: awlme@helix.nih.gov

Electronic identifier: 0960-9822-007-R0082

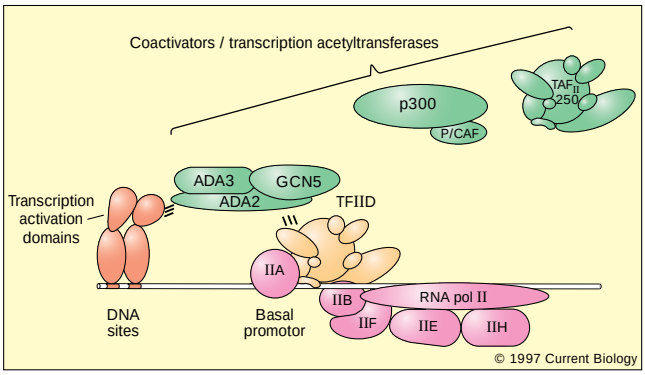
Current Biology 1997, 7:R82–R84

Research on transcriptional control in eukaryotes traditionally takes a two-pronged approach, relying on genetic analysis to define the regulatory elements and transcription factors required to activate or repress a promoter, and on biochemical methods to purify the transcription factors, define their structure and reconstruct their activities *in vitro*. Genetics usually leads the way, but occasionally the biochemists achieve a major breakthrough that reveals unanticipated regulatory mechanisms, and a good example of this has been recently reported.

Early last year, Brownell *et al.* [1] discovered that a previously characterized component of the *Saccharomyces cerevisiae* transcriptional machinery, known as GCN5, acts as a histone acetyltransferase. Metazoan homologs of GCN5 were found to have comparable properties [2]. Now, two other, very different, transcriptional regulators have also been found to acetylate histones [3,4]. These new findings suggest that the modification of histones is a general function of the transcriptional machinery. These transcriptional acetyltransferases have the potential to modulate chromatin conformation continually as a control mechanism for transcription. How might this type of regulation occur?

Transcription is a multistep process with many potential levels of control. An early step is the accumulation on the regulatory elements flanking a gene's transcription start site of sequence-specific DNA-binding proteins that possess transactivation domains. These activation domains recruit coactivators that subsequently facilitate the activity of the basal transcriptional machinery by poorly characterized mechanisms. Excellent examples of this paradigm are transcription factors in *S. cerevisiae* that have acidic activation domains; these domains recruit a trimeric coactivator complex, ADA2–ADA3–GCN5 [5], which in turn contacts the basal transcriptional machinery.

Figure 1

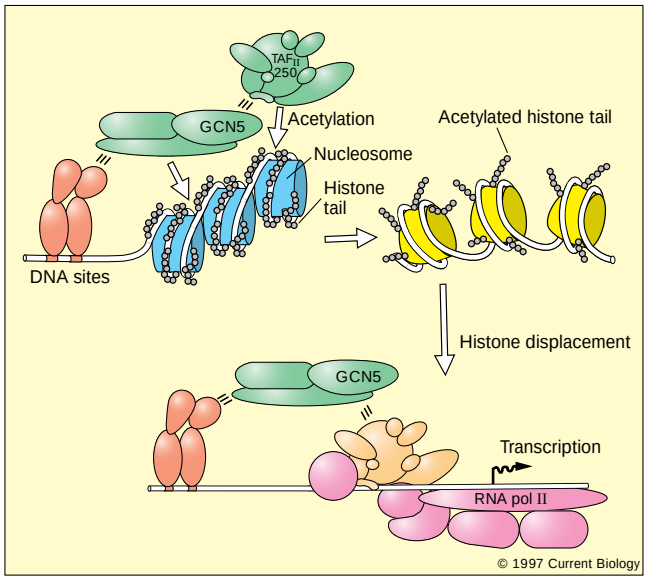


Model 1: transcriptional coactivators interact with both sequence-selective transcription factors and the basal transcription machinery. As discussed in the text, a number of coactivators have recently been found to be histone acetyltransferases; these include GCN5, p300/CBP, P/CAF and $TAF_{II}250$ (green). These proteins, either individually or in combination with other subunits, make contact with the activation domains of transcription factors and help recruit TFIID (orange) or other components of the basal transcriptional machinery (pink). These protein–protein interactions might stimulate transcription independent of any acetylation of the core histones. The $TAF_{II}250$ complex is shown in two different colors to emphasize the multiple functions carried by the same protein.

In metazoans, numerous DNA-binding transcription factors, including steroid receptors, make use of the coactivator p300/CBP [6]. p300/CBP has a domain highly similar in sequence to part of yeast ADA2, and associates with a factor P/CAF that shows significant sequence similarity to yeast GCN5 [2]. These coactivators were proposed to function as scaffolding intermediates that might integrate the functions of distinct transactivation domains within particular DNA-bound factors, which can be present in a large variety of combinations, to increase the efficiency with which the basal transcriptional machinery is recruited to a promoter [5]. This is a useful model (Fig. 1), and it might still be true. However, the discovery that yeast GCN5, human P/CAF and p300/CBP have additional catalytic functions as histone acetyltransferases provides alternative, and potentially more interesting, possibilities.

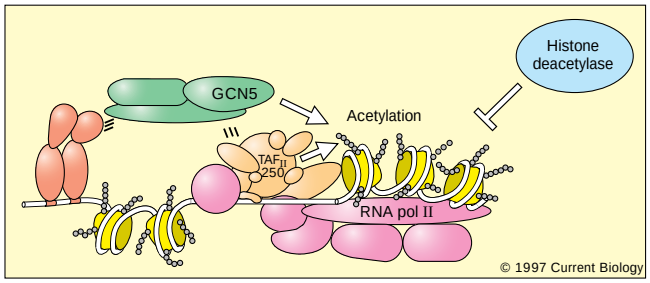
Genetic experiments have unambiguously established that the core histones have a key role in transcriptional regulation [7]. Each core histone has two domains: a histone-fold domain that is involved in histone–histone interactions and in wrapping DNA into nucleosomes, and an amino-terminal domain that lies on the outside of the nucleosome, where it can interact with other regulatory proteins [8]. These histone-associated regulatory proteins include

Figure 2



Model 2: coactivators function as histone acetyltransferases that facilitate the disruption of nucleosomes and recruitment of the basal transcriptional machinery. Recruitment of coactivators that regulate transcription by acetylating histones leads to the modification of repressive nucleosomal structures (blue) in which the histone tails are stably associated with DNA. Acetylation of the histone amino-terminal tails leads to a disruption in nucleosomal structure (blue nucleosomes turn yellow). Histones are displaced from DNA and the basal transcriptional machinery can be recruited by interactions between the coactivator and the basal transcriptional machinery (as in Fig. 1).

Figure 3



Model 3: coactivators and histone deacetylases act continually to regulate transcription. Recruitment of coactivators increases the local level of histone acetylation, partially disrupting nucleosomal structure but without displacing the histone from DNA. The coactivators also facilitate the sequestration of the basal transcriptional machinery to the disrupted chromatin template, where it works very efficiently. Histone deacetylase activity can reverse the action of the coactivators, restoring a repressive chromatin environment. Under the conditions where histones continually compete with the transcriptional machinery, the acetyltransferase activity of the coactivators is continually required for transcription. Variation in histone acetylation level offers the opportunity for a regulated variation in transcriptional activity.

structural components that repress transcription [7], and others that can activate transcription. Among the proteins that can activate transcription are yeast GCN5, human P/CAF and p300/CBP. All of these proteins modify the amino-terminal tails of particular core histones by acetylating lysine residues in the histone tail domains [1–3]. Core histone acetylation destabilizes the nucleosome, so that DNA-binding components of the basal transcriptional machinery can gain more effective access to promoter elements and consequently facilitate transcription [9].

This leads to a second potential model for the transcriptional activation function of the coactivators (Fig. 2). The recruitment of coactivators could direct the local destabilization of repressive nucleosomes that prevent either the association or function of the basal transcriptional machinery on a promoter. Once histones in these nucleosomes are acetylated, the basal transcription machinery might operate more effectively. This model predicts that targeted acetylation provides a means of allowing the basal transcriptional machinery to displace nucleosomes, assemble a functional transcription complex and never have to deal with chromatin again. It allows the amino-terminal tails to contribute to both gene repression in their unacetylated form and to the relief of the repressed state once they are acetylated — but only once. This type of all-or-none modulation necessarily limits the histones to the regulation of transcription complex assembly.

Additional support for this model follows from the fact that another transcription factor that acts as a histone acetyltransferase is a component of the general transcription factor TFIID (Fig. 1, [4]). The $TAF_{II}250$ subunit of TFIID has multiple enzymatic activities: it is a histone acetyltransferase [4] and also a kinase that phosphorylates the RAP74 subunit of TFIIF [10]. The histone acetyltransferase activity of $TAF_{II}250$ leads to the suggestion that TFIID itself comes equipped to modify the core histones and facilitate access of the other basal transcription factors to promoters packaged into chromatin [4]. Nevertheless, for many promoters, the regulation of transcription is not an all-or-none process, but undergoes continual variation. How might such modulation in transcriptional activity be achieved?

Aside from transcriptional regulators that function as histone acetyltransferases, there are also regulators that deacetylate the histones. These deacetylases comprise part of a transcriptional repression pathway conserved from yeast to vertebrates [11,12]. Thus deacetylating histones, either as a targeted event or through a general delocalized activity, is likely to repress transcription or prevent transcriptional activation from occurring at all (Fig. 3). The identification of histone deacetylases as transcriptional regulators provides a molecular mechanism whereby transcription might be continually controlled (Fig. 3). This third model stipulates that the core histone proteins remain associated with DNA in the vicinity of a promoter

in spite of the recruitment of the basal transcriptional machinery.

There is substantial evidence in support of this hypothesis [13]. The recruitment of histone acetyltransferases by DNA-binding transcription factors will lead to acetylation of the core histones, destabilizing the nucleosome and facilitating transcription. If acetylated core histones remain in the vicinity of the promoter, then the targeted or general activity of histone deacetylases will return nucleosomes to their repressive configuration. Thus, the persistence of gene activity would require the continued activity of the transcription acetyltransferases. In this way, transcription could be continually modulated through histone modification. There is excellent precedent for conformation regulating catalytic function; in fact, chromatin conformation and modification have long been correlated with transcriptional activity.

The discovery that transcriptional regulators function as histone acetyltransferases or deacetylases [1,11] further emphasizes the fact that the eukaryotic transcriptional machinery is not only adapted to function in a chromatin environment, but actually makes use of the packaging of DNA into chromatin to regulate genes. It should be noted that GCN5, p300/CBP and $TAF_{II}250$ share little similarity and represent distinct families of acetyltransferases. It is probable that other acetyltransferases exist, and that, in addition to the histones, other components of the transcriptional machinery will be modified through acetylation. Other transcriptional regulators are also likely to post-translationally modify the histones in different ways — for example, by phosphorylation, ubiquitination or ADP-ribosylation. These observations provide an attractive dynamic quality to the roles of the transcriptional regulators in the transcription process. Chromatin structure and modification appear to have a causal controlling role in transcriptional regulation. Determining exactly how this is achieved represents an important challenge for the future.

References

1. Brownell JE, Zhou J, Ranalli T, Kobayashi R, Edmondson DG, Roth SY, Allis CD: Tetrahymena histone acetyltransferase A: a homolog to yeast Gcn5p linking histone acetylation to gene activation. *Cell* 1996, 84:843–851.
2. Yang X-J, Ogryzko VV, Nishikawa J-I, Howard B, Nakatani Y: A p300/CBP-associated factor that competes with the adenoviral E1A oncoprotein. *Nature* 1996, 382:319–324.
3. Ogryzko VV, Schiltz RL, Russanova V, Howard BH, Nakatani Y: The transcriptional coactivators p300 and CBP are histone acetyltransferases. *Cell* 1996, 87:953–959.
4. Mizzen CA, Yang XJ, Kobuko T, Brownell JE, Bannister AJ, Owen-Hughes T, Workman J, Berger SL, Kouzavides T, Nakatani Y, Allis CD: The $TAF_{II}250$ subunit of TFIID has histone acetyltransferase activity. *Cell* 1996, 87:1261–1270.
5. Guarente L: Transcriptional coactivators in yeast and beyond. *Trends Biochem Sci* 1995, 20:517–521.
6. Janknecht R, Hunter T: A growing coactivator network. *Nature* 1996, 383:22–23.
7. Grunstein M, Hecht A, Fisher-Adams G, Wan J, Mann RK, Strahl-Bolsinger S, Laroche T, Gasser S: The regulation of euchromatin and heterochromatin by histones in yeast. *J Cell Sci* 1995, 19:29–36.
8. Wolffe AP, Pruss D: Chromatin: hanging on to histones. *Curr Biol* 1996, 6:234–237.
9. Lee DY, Hayes JJ, Pruss D, Wolffe AP: A positive role for histone acetylation in transcription factor binding to nucleosomal DNA. *Cell* 1993, 72:73–84.
10. Dikstein R, Ruppert S, Tjian R: $TAF_{II}250$ is a bipartite protein kinase that phosphorylates the basal transcription factor RAP74. *Cell* 1996, 84:781–790.
11. Taunton J, Hassig CA, Schreiber SL: A mammalian histone deacetylase related to a yeast transcriptional regulator Rpd3. *Science* 1996, 272:408–411.
12. Ayer DE, Lawrence QA, Eisenman RN: Mad–Max transcriptional repression is mediated by ternary complex formation with mammalian homologs of yeast repressor Sin3. *Cell* 1995, 80:767–776.
13. Nacheva GA, Guschin DY, Preobrazhenskaya OV, Karpov VL, Elbradise KK, Mirzabekov AD: Change in the pattern of histone binding to DNA upon transcriptional activation. *Cell* 1989, 58:27–36.