Sinful repression

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Nature (News and Views) Vol. 387, 16-17, 1997

The structure of chromatin — the material of which eukaryotic chromosomes are composed — presents both problems and opportunities to the transcriptional machinery. Genes are transcribed in the eukaryotic nucleus without apparent impediment, even though the DNA template is wrapped around histone proteins to form nucleosomes and the chromatin fibre. Evolution has been remarkably successful in shaping chromatin such that it can become alternatively transparent or opaque, to facilitate or restrict the access of transcription factors and RNA polymerase to DNA. The molecular mechanisms that control this access are central to gene regulation, and two reports, by Heinzel et al. (1) and Alland et al. (2) on pages 43 and 49 of this issue respectively, along with five related papers in Cell, complete one picture of how gene regulation is controlled.

Nucleosomes are not static entities - they adopt a variety of stability states that are dependent on post-translational modification of the core histones. In particular, acetylation of the histones can destabilize nucleosomes and relieve transcriptional repression by allowing transcription factors access to recognition elements. Conversely, deacetylation of the histones stabilizes the repressed state (3). Last year, certain transcriptional coactivators were found to have histone acetyltransferase activity. So specific targeting of these regulatory complexes could allow nucleosome modification to be directed to particular promoters (4,5).

The CREB-binding protein (p300/CBP) is one such co-activator. It has histone acetyltransferase activity, integrating transcriptional-activation signals from diverse regulatory proteins, including steroid and nuclear-hormone receptors (6). Histone acetylation is targeted by these receptors in response to the addition of ligand (for example, oestrogen and thyroid hormone), rendering the chromatin much more transparent to the transcriptional machinery. Heinzel et al. (1) and Alland et al. (2) now show that histone deacetylation might also be targeted by nuclear-hormone receptors and other transcriptional repressors. The five papers in Cell substantiate these observations, and extend the repertoire of proven and potential regulatory proteins that use similar repression mechanisms (7-11). The emerging picture is one of gene regulation in which reversible alterations in histone chemistry have an important controlling function.

Heinzel et al. (1) report that N-CoR, a known co-repressor for the thyroid-hormone receptor, exists in a complex with the mammalian homologues of two yeast corepressors, Sin3 and RPD3. Sin3 and RPD3 both act in a pathway that accentuates the transcriptional silencing of several yeast genes (12), and RPD3 is a histone deacetylase (13). The authors have done antibody-blocking experiments in microinjected mammalian cells to show that each component of the N-CoR/mSin3/mRPD3 complex is essential for the transcriptional repression that is directed by the unliganded thyroid-hormone receptor. Moreover, this transcriptional repression is greatly potentiated by nucleosome assembly'[4], in agreement with the prediction that the targeted co-repressor will need a nucleosomal template with which to function most effectively through the action ofhistone deacetylase.

Mammalian Sin3 is also a co-repressor for the Mad/Max complex (15). Mad is a sequence-specific DNA-binding helix-loop-helix protein that antagonizes the transcriptional activation and transformation functions of the oncoprotein Myc. Mad acts, in part, by competing with Myc for a common heterodimeric partner, Max. Alland et al. (2) show that mSin3 uses distinct domains to interact with Mad, N-CoR and the mammalian histone deacetylase (mRPD3). This modular series of interactions allows discrimination between the diverse functions of mSin3. Mammalian Sin3 contains four paired, amphipathic helices (PAH1-4). N-CoR associates with PAH1, the Mad-mSin3 association requires PAH2, and mRPD3 associates with the PAH3 and PAH4 domains (2,15). Transcriptional repression by Mad requires only PAH1 and PAH2, whereas suppression of transformation requires PAH3 and PAH4 (ref. 2). Histone deacetylase is only recovered in the co-repressor complex that contains all four helices, suggesting that N-CoR bound to PAR 1-2 might use other mechanisms — in addition to histone deacetylation — to repress transcription. In contrast, the tumour-suppression properties of mSin3 require the full-length protein and associated histone deacetylase. This is particularly interesting because acute myelocytic leukaemia is associated with a chromosomal translocation that fuses the zinc-finger DNA-binding domain of the MOZ (monocytic-leukaemia zinc-finger) gene to the histone acetyltransferase CBP (ref. 16). Deregulated histone acetylation might promote transformation, and the regulated activity of histone deacetylase might contribute to growth control.

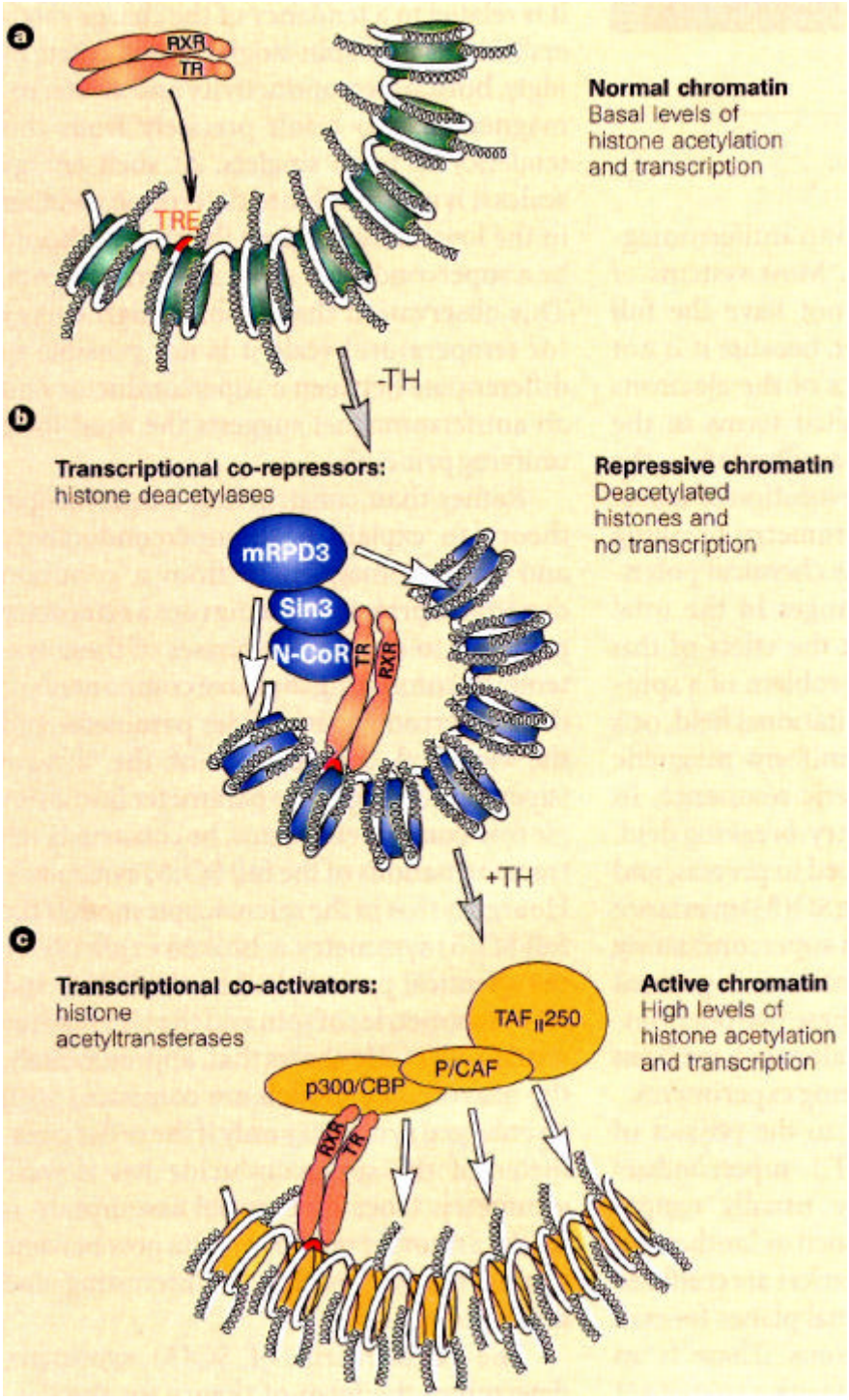

Figure 1 The findings by Heinzel et al. (1) and Alland et al. (2) contribute to a three-step model for transcriptional regulation by the thyroid-hormone receptor. a, Precise rotational positioning of the DNA sequence containing the thyroid-hormone response element (TRE) on the surface of the histone octamer, allows the thyroid-hormone receptor (TRIRXR) access to chromatin (14). b, Once in place, the unliganded receptor recruits a deacetylase complex (mRPD3/Sin3/N-CoR) to augment repression'. c, Subsequent addition of thyroid hormone (TH) leads to recruitment of acetyltransferases (p300/CBP, P/CAF, $TAF_{II}250$) that can disrupt these repressive histone-DNA interactions (5,6,17).

By defining transcriptional repressors as histone deacetylases and transcriptional activators as histone acetyltransferases, the histones and chromatin structure are fully integrated as necessary components of the regulatory machinery. Although the exact biochemical mechanisms are not yet known, a three-step mechanism can now be proposed for transcriptional regulation by the thyroid-hormone receptor (Fig. 1). Normal chromatin has a constitutive level of histone acetylation that allows basal transcription; but, in the absence of thyroid hormone (TH), the thyroid-hormone receptor (TR/RXR) binds to nucleosomal DNA and targets histone deacetylation, thereby repressing transcription. In the presence of thyroid hormone, histone acetyltransferases are recruited to relieve the transcriptional repression.

Targeted acetylation allows the basal machinery to displace nucleosomes, assemble a functional transcription complex and never have to deal with chromatin again. Alternatively, the regulated association and activity of histone acetyltransferases and deacetylases might occur within a common complex. Transcriptional activity could then be continually modulated through variation in the conformation of the chromatin. Histones would remain present throughout the transcription process. Recapitulating these events means that we will have to understand the regulation of an increasingly sophisticated machinery, and an enzymology that is dedicated to communication between the proteins that package DNA and those that use it as a template.

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