New data on nuclear hormone receptor cofactors suggest a control of transcriptional repression by hormone-dependent chromatin remodelling

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Transcriptional activation of genes has been the focus of numerous studies. In eukaryotic cells, the transcription of genes encoding messenger RNA requires RNA polymerase II (PolII) as well as many additional proteins that bind promoter regions and initiate transcription (1). Eukaryotic activators, which bear an activating region and a DNA binding domain, may function by recruiting the components of the transcriptional machinery to the target DNA (1, 2).

Another level of control of gene regulation has been more recently uncovered. The DNA template is wrapped around histone proteins to form nucleosomes and the chromatin fibre. Chromatin alternatively facilitates or restricts the access of the transcriptional machinery to the DNA. The molecular mechanisms that control the access of promoter proteins and PolII to the DNA binding regions are crucial to gene regulation. Nucleosome structure is dynamic in that it adopts different stability states which are dependent upon post-transcriptional modification of the core histones. So far, it had been shown that acetylation of the histones modifies the nucleosome structure and relieves transcriptional repression by allowing the transcriptional machinery to access its DNA template. Interestingly, transcriptional ‘co-activators’, such as cyclic AMP response element binding protein (CREB) binding protein (CBP), were found to have histone acetyltransferase activity; CBP integrates transcriptional activation signals from various stimuli, including the nuclear hormone receptors (3). Therefore, one can envision that specific targeting of these complexes with acetyltransferase activity (and hypothetically with deacetylase activity to induce transcriptional repression) could induce nucleosome modification at particular promoters, ultimately leading to gene transcription. We will see that these assumptions are being substantiated by a series of recent discoveries which increase our understanding of the functioning of the thyroid hormone receptor (4–7). Thyroid hormone triiodothyronine (T3) exerts effects on gene expression upon binding to its receptor (TR). TR is part of a subclass of nuclear receptors that includes the vitamin D receptor, the retinoid receptor, and the prostaglandin receptor superfamily (4). All these receptors may be divided into five regions, based on structure–function similarities, with the central and carboxyl-terminal regions containing the conserved DNA binding domain and the ligand binding domain, respectively (4). TR binds to DNA as a heterodimer with the unoccupied 9-cis retinoic acid receptor (RAR) (retinoid X receptor, RXR), at its hormone response elements (HREs) (4). TR in its unbound state binds to and activates transcription in the case of some thyroid HREs while it represses gene transcription in the case of others thyroid HREs. One of the proteins that mediates this ligand-independent gene transcription repression by the TR (and the RAR) has been cloned and named N-CoR (nuclear receptor corepressor) (8).

Now, it has been shown that N-CoR exists in a protein complex with mSin3 (mammalian Sin3) and a histone deacetylase (HDAC1 or mRpd3), two mammalian homologues of, respectively, yeast corepressor Sin3 and yeast histone deacetylase Rpd3 (5, 7). The authors demonstrated that the complex comprising N-CoR, mSin3 and the histone deacetylase mRpd3 binds to the TR and mediates a ligand-independent transcriptional repression (5). Therefore, a picture of the transcriptional regulation by TR emerges. The heterodimeric TR/RXR unliganded receptor accesses the chromatinized thyroid HRE and, when in place, recruits the deacetylase complex (mRpd3/mSin3/N-CoR) to increase transcriptional repression of the genes under control of the thyroid HRE. Addition of the ligand (T3) leads to the release of the deacetylase complex and the recruitment of acetyltransferases that weaken the repressive histone–DNA interactions. The new picture is that of a level of transcription resulting from the balance between histone acetylation and deacetylation (5, 7, 9).

In addition, another corepressor for the thyroid hormone and the RAR, named SMRT (for silencing mediator for RAR and TR), was described (4). SMRT also interacts, in a similar way to N-CoR, with Sin3A and the histone deacetylase to form a multisubunit repressor complex (7). The view of the thyroid receptor signalling system may even be more complex as alternative forms of N-CoR and SMRT lacking transcriptional repression may compete with the functional repressive forms (4, 7, 10).
Other studies confirmed these findings, using different techniques and extending the set of proteins concerned by these repression mechanisms beyond the nuclear receptors (6, 11–14). A distinct system regulated via repression or activation of gene transcription is the Myc/Mad/Max transcription factors network (12, 13). It is involved in the very fashionable field of research on control of cell differentiation or proliferation, and is the focus of much work. Max is a basic helix–loop–helix leucine zipper protein (bHLH-Zip) that forms DNA binding heterodimers with members of the Myc and bHLH-Zip Mad family (12, 13). The histone deacetylation is the basis of Mad repression (5, 6, 12, 13). Since Mad antagonizes Myc proliferative function both biologically and transcriptionally at Myc–Max binding sites, the results of these recent studies raise the possibility (if Myc may be shown to drive histone acetylation) that a balance between Myc and Mad regulated transcription occurs through the opposing actions of histone acetyltransferases and deacetylases, therefore driving the cell to either a proliferation (eventually oncogenic) or a differentiation pathway (5, 6, 12, 13).

This mechanism of transcriptional repression, using histone deacetylation, has also been found in yeasts, emphasizing the conservation of these control mechanisms through the eukaryotes (14). This expands clearly the interest of the studies beyond the endocrinology field. However, it does remain to be established definitely: (i) that the histones are the targets of the acetylation/deacetylation reactions within those systems; (ii) what is the relative role of those modifications compared with other post-translational histone modifications, such as phosphorylation for example; and (iii) what is the precise mechanisms, which are only speculative so far, by which the histone acetylation/deacetylation could affect transcriptional activity (15). Moreover, the evidence for transcriptional modulation through local histone modification is so far purely inferential and direct functional data are currently lacking. The role of tissue-specific expression of cofactor remains also to be determined as it can have important consequences in terms of drug design, aiming at tissue-specific action, as in the case of the partial oestrogen agonist raloxifene. This drug has oestrogen agonist like action on bone tissues and serum lipids while displaying potent oestrogen antagonist properties in the breast and uterus (16). Nevertheless the wealth of new information coming from independent groups working on different systems adds credence to the fact that transcriptional repression controlled by acetylation/deacetylation of the histones may be crucial in nuclear hormone receptor function to remodel chromatin in a hormone-dependent fashion and besides on the control of the differentiation versus proliferation pathways in cells.

References
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