CHROMATIN

# Gene dimmer switch

Nucleosome remodelling and deacetylation (NuRD) is a chromatin remodelling complex with two distinct enzymatic activities: histone deacetylation by its subunits HDAC1 and HDAC2 and nucleosome remodelling by CHD4. The two NuRD modules are linked by MBD3. NuRD is widely distributed at sites of active transcription, where it controls nucleosome density at regulatory sequences. Bornelöv et al. investigated the individual enzymatic activities of NuRD and their roles in regulating transcription.

Genome-wide analysis of NuRD components mapped CHD4 and MBD3 predominantly to sites of active transcription, but surprisingly MBD3 depletion and consequently impairment of NuRD complex formation in mouse embryonic stem cells (mESCs) caused only modest changes in gene expression. This suggests that NuRD may be involved in fine-tuning, instead of acting as an on–off switch, of gene expression.

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To study how NuRD regulates gene expression, the authors engineered inducible NuRD activation in mESCs by fusing MBD3 with the oestrogen receptor. Addition of the oestrogen-receptor ligand tamoxifen induced MBD3 translocation to the nucleus, NuRD complex formation and transcriptional changes and restored differentiation potential.

The addition of tamoxifen caused changes in histone acetylation only 48 h after MBD3-dependent formation of the NuRD complex on chromatin and after the occurrence of transcriptional changes. Conversely, changes in nucleosome positioning were observed shortly after NuRD complex formation. This suggests that the chromatin remodelling activity (and not the deacetylation activity) of NuRD is the primary cause of the observed transcriptional changes.

Intriguingly, NuRD-dependent increase in nucleosome density led to clearance of chromatin-bound proteins, which then allowed binding of a new set of proteins at these sites. Specific MBD3-dependent effects at promoters and enhancers also resulted in dissociation of the transcription machinery and transient reduction of nascent RNA levels, resulting in either increased or decreased gene expression.

Finally, NuRD maintained suitable nucleosome structure and protein binding at regulatory sequences of specific genes undergoing differentiation-induced transcriptional changes.

In summary, the data indicate that NuRD is capable of fine-tuning gene expression by modulating nucleosome density, leading to both gene activation and repression. The determinants of the different outcomes remain unclear.

*Anne Mirabella, Associate Editor,*
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**ORIGINAL ARTICLE** Bornelöv, S. et al. The nucleosome remodeling and deacetylation complex modulates chromatin structure at sites of active transcription to fine-tune gene expression. *Mol. Cell* **71**, 56–72 (2018)
**FURTHER READING** Clapier, C. R. et al. Mechanisms of action and regulation of ATP-dependent chromatin-remodelling complexes. *Nat. Rev. Mol. Cell Biol.* **18**, 407–422 (2017)

# Journal club

## AN ELEGANT UPR DISCOVERY

I wish I could say that I've never cited a paper I haven't read, but sadly, it wouldn't be true. There are certain landmark papers that are just too easy to cite, following the lead of previous papers, without ever reading much more than the title. It is a mistake, of course. Papers often become landmarks not only for the data reported, but also for the unique, forward-thinking and insightful interpretation of those data. They can also be useful reminders of the power of traditional experimental approaches. This is the case for the seminal paper by Cox and Walter, reporting the identification of HAC1 as a key regulator of the unfolded protein response (UPR).

As a newcomer to the UPR, I cited Cox and Walter several times before I ever read beyond the abstract. When I finally did — feeling, guiltily, that I should probably know a bit more about the history of my new field — I was so impressed by its elegance and insight that I've never taken it for granted since.

By 1996, when the paper was published, the basic mechanism of the UPR had been laid out. This was a transcriptional response, activating a conserved promoter sequence to increase the expression of genes that included the protein chaperone BiP, and that required the kinase IRE1. The 'missing piece' was a transcription factor.

Cox and Walter searched for this transcription factor using a sensitive and elegant yeast genetics approach — a good reminder of the power of classical yeast genetics. They screened, in an *ire1* deletion background, for genes that could activate *HIS3* (a gene necessary for cell survival) under the control of four copies of the UPR-responsive element (UPRE). They identified three genes: *IRE1*, *SWI4* (encoding a transcription factor that is part of the general transcription machinery) and *HAC1*. *HAC1* encoded another putative transcription factor that proved to be necessary to activate the UPR. It could also rescue *ire1* mutants, and bound directly and specifically to the UPRE, fulfilling all the criteria for a UPR transcription factor. But how was *HAC1* regulated?

The HAC1 protein seemed to appear only following UPR induction, despite the constitutive presence of its mRNA. Surprisingly, though, a new, shorter *HAC1* RNA species was detected upon endoplasmic reticulum stress. Using primer extension, then cloning and sequencing (a reminder of how laborious such things used to be!) they found that this RNA was missing an internal sequence, identical in all the clones they tested. This finding provided a key insight: the *HAC1* mRNA was spliced upon UPR induction! Splicing created a stable protein that was capable of inducing the UPR.

Confusingly, however, the *HAC1* RNA did not contain consensus splice sequences. Undiscouraged, the Walter laboratory pursued their splicing theory. By the following year, they had determined that IRE1 could splice *HAC1* directly, in the cytosol, through its C-terminal tail domain.

This remains a unique activation mechanism, and re-reading these papers gives me a powerful sense of how exciting the discoveries must have felt at the time. For me, they represent a reminder of the continued relevance of classical genetics, the insight it takes to spot a novel mechanism and the value of knowing your history.

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**ORIGINAL ARTICLES** Cox, J. S. & Walter, P. A novel mechanism for regulating activity of a transcription factor that controls the unfolded protein response. *Cell* **87**, 391–404 (1996) | Sidrauski, C., Cox, J. S. & Walter, P. tRNA ligase is required for regulated mRNA splicing in the unfolded protein response. *Cell* **87**, 405–413 (1996) | Sidrauski, C. & Walter, P. The transmembrane kinase Ire1p is a site-specific endonuclease that initiates mRNA splicing in the unfolded protein response. *Cell* **90**, 1031–1039 (1997)