CELL DIVISION

Foreman in the histone factory

The cell, like any factory, must often step up supply to meet demand. For example, during S phase of the cell cycle, the supply of histones has to be increased to decorate the newly synthesized DNA. Two papers in *Genes and Development* explain how the kinase CDK2 and its regulatory partner cyclin E coordinate the synthesis of histones and DNA through a CDK2 substrate called NPAT.

Humans have two clusters of histone genes, on chomosomes 1 and 6, but the transcription factors driving histone expression vary. Zhao and colleagues reasoned that there must be a 'master regulator' of histone expression and set out to find it. Having previously identified NPAT in a screen for cyclin E–CDK2 substrates, they used immunofluorescence to study its cellular localization. This revealed two tiny dots of NPAT in non-S-phase cells, but four in S phase. This localization overlapped with that of coilin, a component of a nuclear organelle called the Cajal body or coiled body (see picture) — a finding corroborated by Ma and colleagues. Cajal bodies often associate with histone gene clusters, so this finding provided an intriguing link between cyclin E–CDK2 and histone genes. Furthermore, fluorescence *in situ* hybridization showed that NPAT's association with the histone gene cluster on chromosome 1 was cell cycle dependent, explaining why the number of NPAT dots increases during S phase.

Next, Zhao *et al.* found a large increase in gene expression driven by the histone H4 promoter when the *NPAT* gene was cotransfected into the cells. NPAT also enhanced expression from the H2B and H3 promoters. For the H4 promoter, the authors narrowed down the NPAT-responsive region to a sequence that binds a putative transcription factor called H4TF-2. Mutations in this sequence that abolish H4TF-2 binding blocked the effect of NPAT, whereas cotransfection of cyclin E- and CDK2-expressing plasmids enhanced NPAT-mediated transcriptional activation of histone genes.

Ma and colleagues determined the CDK2 phosphorylation sites on NPAT, then used phospho-NPAT-specific antibodies to show that phospho-NPAT colocalizes with both cyclin E and coilin in Cajal bodies, and that the combination of phospho-NPAT and cyclin E–CDK2 is present in Cajal bodies only during S phase. Furthermore, mutation of NPAT's CDK2 phosphorylation sites to alanine reduced NPAT's ability to activate transcription from the histone 2B promoter.

So cyclin E–CDK2 gives the orders, and NPAT ensures that they're carried out. Appreciating NPAT's skills will be our next lesson in this tour of the histone factory: how does NPAT manage its staff — presumably the histone-gene-specific transcription factors — and does it have other teams with responsibilities beyond histone production?

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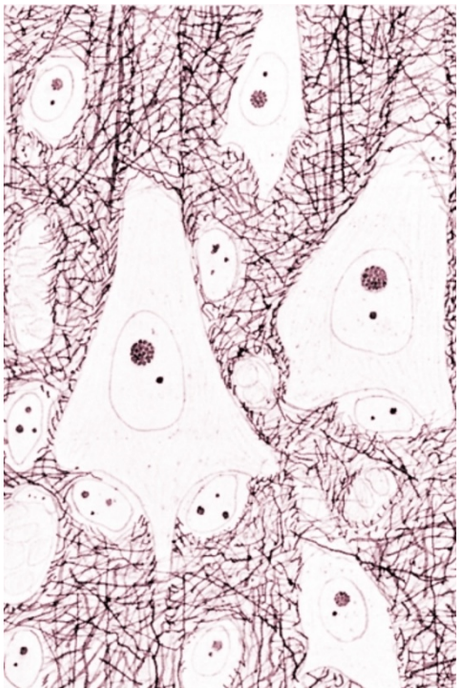

One of Cajal's drawings of his 'accessory bodies', from a paper published in 1910. This organelle was then forgotten for 60 years until it was rediscovered and named the coiled body by W. Bernard. Image courtesy of Joseph Gall, Carnegie Institution, Baltimore, Maryland, USA.

References and links

ORIGINAL RESEARCH PAPERS Zhao, J. *et al.* NPAT links cyclin E–Cdk2 to the regulation of replication-dependent histone gene transcription. *Genes Dev.* **14**, 2283–2297 (2000) | Ma, T. *et al.* Cell cycle-regulated phosphorylation of $p220^{NPAT}$ by cyclinE/Cdk2 in Cajal bodies promotes histone gene transcription. *Genes Dev.* **14**, 2298–2313 (2000)

FURTHER READING Ewan, M. E. Where the cell cycle and histones meet. *Genes Dev.* **14**, 2265–2270 (2000)