NUCLEAR TRANSPORT

How to get out

Nuclear transport is coordinated by nuclear Ran•GTP, which releases cargo from importin proteins and promotes cargo binding to exportin proteins. The role of Ran•GTP in cargo release is reasonably well understood. But, how does Ran•GTP function in nuclear protein export to promote cargo binding? Matsuura and Stewart now provide insights by describing the 2.0-Å resolution crystal structure of a nuclear export complex in *Nature*.

The nuclear export complex comprised Ran•GTP, Cse1 (a yeast exportin) and Kap60. Kap60 is an adaptor protein (yeast importin-α) that binds to nuclear localization signal (NLS)-containing cargo proteins and links them to Kap95 (yeast importin-β) in the cytoplasm. Following protein import, Kap60 is exported from the nucleus as Cse1 cargo. A notable feature of the structure — which is different to that seen for nuclear import complexes — is that Cse1 surrounds Ran•GTP and Kap60. Cse1 interacts with Ran•GTP at two distinct sites, effectively locking it in the GTP-bound state. The Kap95-binding domain of Kap60 is also able to bind to the NLS-binding sites of Kap60 in an autoinhibitory manner and, in the nuclear export complex, this domain is clamped to the Kap60 NLS-binding sites by Ran•GTP and Cse1. The fact that this intramolecular interaction in Kap60 is required for Cse1 binding ensures that only cargo-free Kap60 is exported.

Mutagenesis studies confirmed the importance of Kap95-binding-domain interactions in nuclear-export-complex assembly and Kap60 export. In addition, the study of other mutant proteins indicated that free Cse1 adopts a different conformation to that seen in the nuclear export complex. It seems that Kap60 binding distorts Cse1 into a high-energy, strained conformation, such that the nuclear export complex is spring-loaded for disassembly following GTP hydrolysis in the cytoplasm.

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References and links

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FURTHER READING Hoelz, A. & Blobel, G. Cell biology: popping out of the nucleus. *Nature* **432**, 815–816 (2004)

WEB SITE

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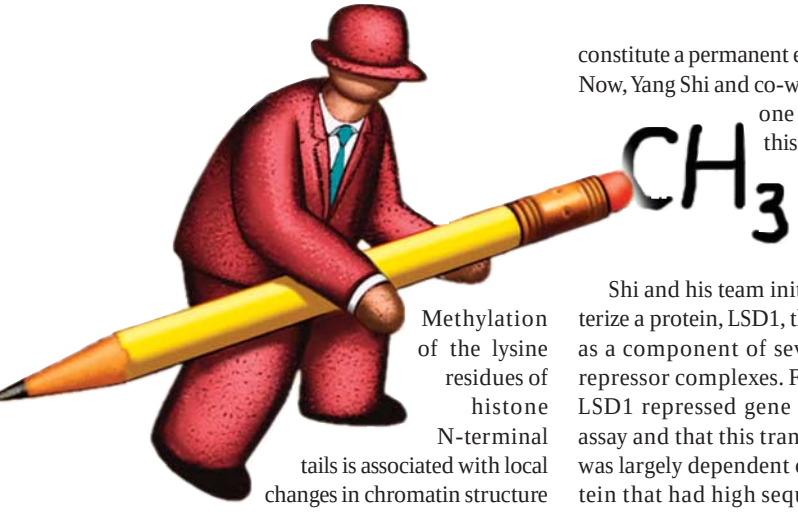
EPIGENETICS

Erasing the mark



Methylation of the lysine residues of histone N-terminal tails is associated with local changes in chromatin structure and correlates with both gene activation and gene repression. The regulation of genes is, however, a dynamic process, and cells must therefore possess the ability to rapidly generate and erase the 'methyl mark'. Whereas several histone methyltransferases have been documented, the identification of an enzyme that removes the methyl group from histone tails has remained elusive, which has fuelled the debate that histone methylation might constitute a permanent epigenetic modification. Now, Yang Shi and co-workers have brought us one step closer to resolving this question by the identification of a histone lysine demethylase, and they report this finding in *Cell*.

Shi and his team initially set out to characterize a protein, LSD1, that had been identified as a component of several transcriptional-repressor complexes. First, they showed that LSD1 repressed gene activity in a reporter assay and that this transcriptional repression was largely dependent on a region of the protein that had high sequence homology with amine oxidases — metabolic enzymes that are putative histone demethylases. This indicated that LSD1 might repress transcription by catalysing the demethylation of core histones.

Direct demethylation assays confirmed that LSD1 removed the methyl group from dimethyl and monomethyl histone H3-K4, but not from trimethyl H3-K4, H3-K9 or several other methylated lysine and arginine residues. H3-K4 methylation correlates with transcriptional activity, and so it is appropriate that a transcriptional repressor would erase this modification.

Because of its homology to the amine oxidases, the researchers predicted that an LSD1-mediated demethylation reaction would generate formaldehyde. Indeed, when LSD1 was incubated with dimethylated substrate in a spectrophotometric assay, large amounts of formaldehyde were detected. This finding provided further compelling evidence that LSD1 was a bona fide demethylase.

But does LSD1 repress endogenous genes by catalysing histone demethylation? The enzyme is found in the Co-REST complex — a transcriptional repressor that silences neuron-specific genes. LSD1-deficient HeLa cells that were generated by RNA interference aberrantly expressed several neuron-specific target genes, and chromatin-immunoprecipitation analyses detected both a loss of association of LSD1 and an increase in H3-K4 methylation at the promoters of these derepressed genes.

So, it seems that a lysine demethylase has at last been pinned down. It is important to note, however, that an enzyme that removes the methyl marks that identify heritably silenced chromatin still defies detection…

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References and links

ORIGINAL RESEARCH PAPER Shi, Y. *et al.* Histone demethylation mediated by the nuclear amine oxidase homolog LSD1. *Cell* **119**, 941–953 (2004)