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GENE REGULATION

The nuclear pore — a scaffold for inducible genes

The nuclear pore complex (NPC) is known to directly interact with chromatin and to influence transcription, but the mechanistic roles of its subunits in regulating gene expression were unclear. Pascual-Garcia *et al.* now show that NPCs can bind to inducible genes and that its components mediate enhancer–promoter looping at these genes.

The NPC is composed of ~30 different nucleoporin (Nup) subunits, some of which are stable (they form the core complex and remain bound to the nuclear envelope), whereas others are dynamic (they can disassociate from the NPC and interact with chromatin independently). The authors carried out chromatin immunoprecipitation followed by sequencing (ChIP–seq) analysis of the dynamic Nup98 in *Drosophila melanogaster* S2 cells and identified 2,214 binding sites; 74% of Nup98 binding sites were at promoters and 17% were at enhancers. To examine Nup binding *in vivo*, brains were isolated from *D. melanogaster* larvae and subjected to ChIP–seq analysis to probe the binding of both stable and dynamic Nups. Again, Nups displayed widespread genome binding, including to enhancers.

Previous work in yeast had suggested that Nups may have a role in the generation of long-range genomic contacts, such as promoter–enhancer pairs. To test this hypothesis, the 3D folding of ecdysone-inducible genes (*Eip74* and *E23*) in response to transcriptional induction with ecdysone in S2 cells was analysed using a chromosome conformation capture (3C) assay. In control cells, *Eip74* enhancer–promoter binding was strongly enhanced upon ecdysone treatment. Notably, this effect was lost upon depletion of Nup98 by RNA interference (RNAi). A similar response seen with the *E23* gene also suggested that Nup98 facilitates the formation of enhancer–promoter contacts.

Ecdysone-inducible genes exhibit transcriptional memory (when a recently activated gene becomes primed for future activation). Interestingly, RNAi-mediated depletion of Nup98 did not affect the first induction of transcription with ecdysone, but reduced activation at the second induction. This finding suggests that Nup98 is involved in transcriptional memory. Furthermore, fluorescence *in situ* hybridization showed that *Eip74* and *E23* localize to the nuclear periphery, regardless of their transcriptional state. Last, co-IP analysis demonstrated that Nup98 interacts with architectural proteins (which mediate 3D genome organization), such as CTCF, and these interactions increased upon transcriptional activation.

In summary, the study suggests that inducible genes associate with NPCs, which may function as a scaffold for silent or poised genes, with its Nup subunits ready to mediate and stabilize enhancer–promoter binding upon gene activation. It remains to be seen to what extent Nups are involved in gene expression during development and cell differentiation.

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> “Nup98 is involved in transcriptional memory”

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ORIGINAL ARTICLE Pascual-Garcia, P. *et al.* Metazoan nuclear pores provide a scaffold for poised genes and mediate enhancer–promoter contacts. *Mol. Cell* http://dx.doi.org/10.1016/j.molcel.2017.02.020 (2017)