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BRAND X PICTURES

CHROMATIN

Drivers of nuclear organization

The organization of eukaryotic nuclei is conserved: heterochromatin, poorly transcribed and late-replicating chromatin domains are usually located at the nuclear periphery, whereas actively transcribed loci and early-replicating domains have more central locations. However, it remains unclear whether changes in position of chromatin relative to the nuclear envelope are a cause or a consequence of gene regulation. Data from Bickmore and colleagues now suggest that chromatin remodelling is sufficient to induce nuclear reorganization.

The authors studied three genes (pleiotrophin (*Ptn*), *Sox6* and neuropilin 1 (*Nrp1*)) that are transcriptionally upregulated, and that move from the nuclear periphery to the centre, during the differentiation of mouse embryonic stem (ES) cells to neural precursor cells (NPCs). To understand the relationship between nuclear reorganization and transcription, the three genes were ectopically expressed using synthetic transcription factors containing TALE (transcription-activator-like effector) DNA-binding domains specific for each promoter fused to a transcriptional activator domain (VP64). Transfection of these transcription factors in ES cells activated *Ptn*, *Sox6* and *Nrp1* and induced the relocalization of the targeted loci from the periphery to the centre of ES cell nuclei. These observations suggest that forced gene expression induces relocalization to the nucleus centre independently of differentiation.

Next, the authors replaced the transactivation domain of the TALE transcription factor with an acidic peptide that decondenses chromatin of target loci without activating transcription. Interestingly, chromatin decondensation at *Ptn*, *Sox6* and *Nrp1* (which was similar to that observed during ES cell differentiation) was sufficient to induce the relocation of each locus towards the centre of nuclei, indicating that nuclear reorganization is driven by chromatin remodelling.

As *Ptn*, *Sox6* and *Nrp1* activation during ES cell to NPC differentiation is normally accompanied with a shift of replication timing from late to early S phase, the authors analysed how TALE transcription factor transfection affects replication timing at these loci. TALE fused to VP64 advanced replication timing, whereas TALE fused to the acidic domain had no effect, suggesting that the switch to early replication requires transcriptional activation.

Thus, this study indicates that nuclear reorganization during differentiation is a consequence of chromatin regulation and that changes in replication timing are a direct consequence of transcription. Further studies should provide insights into the chromatin modifications that are associated with these changes.

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ORIGINAL RESEARCH PAPER Therizols, P. *et al.* Chromatin decondensation is sufficient to alter nuclear organization in embryonic stem cells. *Science* **346**, 1238–1242 (2014)