CHROMOSOMES

Architectural cohesin

the stability of cohesin–DNA interactions has an architectural role in the organization of interphase chromosomes

Fluorescent light micrograph of nuclei from *Wapl*-deficient cells that show 'vermicelli'. The nuclei have been pseudo-coloured and scaled to different sizes. Image courtesy of J.-M. Peters, Research Institute of Molecular Pathology (IMP) Vienna, Austria.

Cohesin is a protein complex that forms a ring around DNA strands to ensure sister chromatid cohesion, which is necessary for proper chromosome segregation during mitosis. Cohesin also associates with DNA during interphase, and this has been suggested to affect chromosome architecture and gene expression. However, the role of cohesin in this context and how this might be regulated are generally unknown. Now, two studies provide new insights into these aspects of cohesin function.

Tedeschi *et al.* studied how WAPL, which is known to mediate the removal of cohesin from chromosome arms during mitotic prophase, might affect cohesin–DNA association and chromosome structure during interphase. Deletion of *Wapl* in mouse embryonic fibroblasts (MEFs) that were arrested in a quiescent state increased the chromatin residence time of cohesin by more than 20-fold, indicating that WAPL is necessary for the removal of cohesin from chromatin. Interestingly, the

increased residency time of cohesin at these sites in *Wapl*-deficient cells led to the condensation of chromatin and to the clustering of cohesin into elongated 'vermicelli'-like structures. The authors observed that each chromosome contained one of these structures, which was consistent with the possibility that the chromosomal 'axis' formed might structurally organize chromatin. So, the authors speculate that in *Wapl*-deficient cells the stabilization of cohesin on DNA promotes cohesin clustering and interphase chromosome condensation through either enhanced cohesin–cohesin interactions or through the stabilization of chromatin loops.

Tedeschi *et al.* also found that WAPL deficiency interfered with exit from quiescence and/or progression through the G1 phase of the cell cycle, which they showed was partly due to decreased expression of the cell cycle transcription factor MYC. This was due to the depletion of WAPL, which was found to affect the expression of numerous genes through either upregulation or downregulation. Further analysis showed that the changes in gene expression were accompanied by changes in cohesin association with transcription start sites (lower for upregulated genes and higher for downregulated genes). This suggests that WAPL-dependent regulation of DNA–cohesin interactions might contribute to the control of gene expression, although the underlying mechanisms remain to be determined.

Yan *et al.* provide further insights into the role of cohesin in gene regulation. They carried out a large-scale analysis of the DNA-binding

patterns of more than 100 expressed transcription factors, as well as of cohesin and of proteins that function to load cohesin onto chromatin. This revealed that DNA binding occurs in dense clusters of up to 100 transcription factors and suggests that the *cis*-regulatory regions cover less than 1% of the human genome — a degree of clustering higher than previously appreciated. Interestingly, almost all clusters contained cohesin. The authors further confirmed the previous observation that the presence of cohesin was associated with an increased DNA sensitivity to DNase I treatment, which is indicative of DNA being more accessible, and they speculate that this situation favours transcription factor binding and gene expression. Because cohesin remains bound to these cluster sites during DNA replication (S phase) and chromosome condensation (early M phase), the authors propose that cohesin might contribute to a transcriptional memory during the cell cycle by facilitating the reloading of transcription factors to cluster sites.

These studies show that the stability of cohesin–DNA interactions has an architectural role in the organization of interphase chromosomes and that such interactions facilitate the binding of transcription factors to specific sites. Whether cohesin retention during mitosis and DNA replication does indeed function to confer transcriptional memory remains to be confirmed.

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ORIGINAL RESEARCH PAPERS Tedeschi, A. *et al.* Wapl is an essential regulator of chromatin structure and chromosome segregation. *Nature* <http://dx.doi.org/10.1038/nature12471> (2013) | Yan, J. *et al.* Transcription factor binding in human cells occurs in dense clusters formed around cohesin anchor sites. *Cell* **154**, 801–813 (2013)