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GENOME ORGANIZATION

Tracking chromosomal conformation through the cell cycle

> Chromosome conformation was not stable in any phase of the cycle

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How chromosome organization changes during the cell cycle has been notoriously difficult to characterize owing to technical limitations, with most studies focusing on interphase nuclei. A new study reports single-cell genome conformation data for hundreds of cells in different phases of the cell cycle and uses a novel *in silico* cell-cycle phasing method to characterize chromatin conformation dynamics throughout the cell cycle.

Genome structure has been shown to be organized in a compartmentalized and hierarchical manner. Three levels of organization have emerged: loops created by the interaction between neighbouring genomic regions; topologically associating domains (TADs) of self-interacting, fairly insulated regions; and compartments, which are groups of TADs containing actively expressed genes or inactive regions.

Nagano *et al.* used flow cytometry cell sorting on mouse embryonic stem cells followed by multiplexed high-resolution chromosome conformation capture (Hi-C) to generate conformation data for 1,992 individual cells at all stages of the cell cycle. Using these single-cell maps, the authors developed a computational strategy to place each of the nuclei in the different phases of the cell cycle. Chromosome conformation was not stable in any phase of the cycle, but instead it changed dynamically throughout.

In general, chromatin compaction increases as cells progress through the cell cycle into mitosis. After mitosis, chromatin unfolding occurs until replication starts, when chromatin starts to compact again. Surprisingly, the different hierarchical domains behaved differently during the cell cycle. Chromatin loops were found to be mostly stable throughout interphase but were not observed during mitosis. By contrast, "we saw quite a dramatic expansion of the TADs that contain active genes as cells come out of mitosis into the G1 phase," recounts Peter Fraser, who led the study together with Amos Tanay. TAD boundaries started to disappear after the G1 phase, with increased contacts being detected across TAD boundaries. Compartments showed the opposite behaviour, increasing as the cell cycle progressed, with chromosomes reaching peak compartmentalization at the end of the S phase. These results are in line with recent studies that found that compartments and TADs are organized independently of each other.

Recent single-cell Hi-C studies have called into question the existence of TAD boundaries, which were first identified in Hi-C studies using pooled populations of cells, suggesting instead that observed boundaries result from the sum of feeble interactions across multiple cells. The work by Nagano *et al.* now provides important evidence for the existence of TADs in individual cells.

"We can now study other potentially dynamic processes such as development and differentiation time courses and observe how the genome organization of thousands of individual cells changes at each step, giving us unique insights that are hidden when one averages over populations of cells," concludes Fraser.

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ORIGINAL ARTICLE Nagano, T. *et al.* Cell-cycle dynamics of chromosomal organization at single-cell resolution. *Nature* **547**, 61–67 (2017)
FURTHER READING Bonev, B. & Cavalli, G. Organization and function of the 3D genome. *Nat. Rev. Genet.* **17**, 661–678 (2016) | Müller, S. & Almouzni, G. Chromatin dynamics during the cell cycle at centromeres. *Nat. Rev. Genet.* **18**, 192–208 (2017)