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GENOME ORGANIZATION

A vision of 3D chromatin organization

DNA is wrapped around nucleosomes to form chromatin chains that can undergo further compaction to fit into the small space of a nucleus. The way chromatin is packaged in the 3D nucleus is crucial to its function; however, owing to the technical challenge of visualizing chromatin in intact cells, what compact chromatin looks like *in vivo* has been the subject of debate for decades. O'Shea and colleagues have now developed a new imaging technique — ChromEMT (chromatin electron microscopy tomography) — that enables the visualization of both the local polymer structure and the global 3D organization of chromatin in the nucleus of intact interphase and mitotic human cells, challenging textbook models of chromatin organization.

Chromatin structure has been difficult to visualize in the nucleus with existing electron microscopy (EM) techniques owing to the lack of a high contrast and selective electron-dense stain that enables it to be distinguished from other components. The authors developed a DNA-labelling system (ChromEM), which uses a fluorescent DNA-binding dye (DRAQ5) that, upon excitation, catalyses the deposition of diaminobenzidine polymers on the surface of DNA, thus making it visible by EM. ChromEM in combination with multi-tilt EM tomography, in which large 3D cell volumes are imaged and reconstructed at multiple angles, enabled the direct visualization and reconstruction of chromatin structure and interactions inside the nucleus.

The chromatin in interphase nuclei was found to be organized into flexible and disordered chains that range from 5 nm to 24 nm in diameter. Interestingly, this organization was seen throughout the nucleus, encompassing euchromatic and heterochromatic regions alike. Moreover, chromatin in mitotic chromosomes had a similar disordered structure and diameter range. This finding challenges the long-standing model of chromatin compaction whereby DNA-wrapped nucleosomes progressively fold into discrete higher-order chromatin fibres and ultimately into mitotic chromosomes. This hierarchical model predicts the formation of 30 nm (although there has been some controversy around this) and 120 nm fibres in interphase nuclei and of more compact 300 nm and 700 nm fibres in mitotic chromosomes.

Instead, O'Shea and colleagues propose that the overall primary structure of chromatin does not change. Different levels of compaction — that generate 3D nuclear domains in which DNA is more or less concentrated and thereby accessible — are achieved by bending flexible fibres at various lengths and creating contacts between and within chains. In mitotic chromosomes, the 3D concentration density of chromatin and such interactions is higher. This model is more plausible when considering the rapid dynamics of chromatin condensation that occur during mitosis.

In addition to prompting the revision of textbooks, ChromEMT opens up the possibility of studying how chromatin structure is linked to its function.

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“chromatin in interphase nuclei was found to be organized into flexible and disordered chains”

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