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Exploration of chromatin structure at molecular resolution *in situ*

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Chromosome organization at the nucleosome level influences nuclear activities like transcription, replication, recombination, and chromosome segregation. The decades-old 30-nm-fiber model posits that the majority of nucleosomes are densely packed into helical fibers, thereby regulating access to DNA sequence and key histone motifs. In the past decade, a few groups including ours have not found any evidence that supports the 30-nm fiber model *in situ*. How, then, do nucleosomes pack inside cell nuclei? The answer to this question requires the three-dimensional visualization of cells at just a few nanometers resolution, in the absence of fixation or staining artifacts. Electron cryotomography (cryo-ET) is a form of cryo-EM that can achieve 4 - 6 nm resolution for “unique” entities such as cells. We have taken advantage of advances in cryo-ET to explore the *in situ* organization of chromatin in the single-celled eukaryotes picoplankton, budding yeast, and fission yeast. In these organisms, nucleosomes do not pack with any short-range order, even at the di-nucleosome level. Furthermore, there are no nuclear bodies that resemble topologically associated domains, which are depicted in the literature as compact globular structures. Instead, chromatin is organized as much-smaller clusters containing fewer than 100 nucleosomes. In mitotic fission yeast, the nucleosome clusters become slightly larger, but the chromosomes do not condense into monolithic structures. Mitotic chromatin is porous, with large ribosome-sized macromolecular complexes and small nucleosome-free pockets interspersed within. Therefore, chromatin structure is permissive to high levels of transcription throughout the cell cycle and it enables the regulation of expression programs without large-scale changes in nucleosome packing.

Artwork by Ann Nee, DBS, NUS