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Journal club

A SILENT REVOLUTION IN CHROMOSOME BIOLOGY

The iconic X shape of mitotic chromosomes is familiar to all. In a human cell, several metres of DNA are packed into micrometre-sized chromosomes, a packaging task that is difficult to explain on the basis of simple intuition.

The classic and still widely used textbook model of a chromosome invokes hierarchical coiling: first, DNA coiling around nucleosomes; second, coiling of the nucleosome strand into a '30 nm fibre'; third, coiling of the 30 nm fibre into higher-order loops that fill the volume of the chromosome. A proteinaceous chromosome scaffold was believed to anchor the DNA loops. Although these models enshrined treasured twentieth century ideas, molecular explanations for the scaffold and hierarchical folding remained elusive.

Diligent biophysicists and microscopists endeavoured to probe what lay inside chromosomes, which led to a silent revolution in chromosome biology. In 2002, Michael Poirier and John Marko measured the physical properties of chromosomes by holding them between two micropipettes. Chromosomes were found to be elastic, and enzyme treatments indicated that the DNA contributed to the elasticity as much as the proteins. This excluded the possibility that chromosomes were shaped by a proteinaceous scaffold, and suggested that they have properties of a DNA–protein meshwork.

A few years later, David Agard, John Sedat and colleagues imaged snap-frozen chromosomes using electron microscopy tomography, and saw what Poirier and Marko had proposed. Chromatin fibres criss-crossed the chromosome and were interlinked at frequent intervals. The condensin protein complex was found at these interlinks, which suggests that this fundamental chromosome constituent may function as crosslinker of the meshwork. Around the same time, Mikhail Eltsov *et al.* observed native chromosomes by cryo-electron microscopy, which revealed the clear signature of nucleosome chains but not of a 30 nm fibre. Using small angle X-ray scattering, Kazuhiro Maeshima and colleagues again observed nucleosomes but no other repeating structures at a greater scale, and therefore found no evidence of a folding hierarchy.

Thus, a chromosome is probably the result of a self-organizing nucleosome chain, which is constrained by condensin-mediated interactions. We may already know all it takes to make a chromosome, but the sheer scale of it remains beyond our imagination.

Frank Uhlmann
Chromosome Segregation Laboratory, Cancer Research UK, London Research Institute, 44 Lincoln's Inn Fields, London WC2A 3LY, UK
e-mail: frank.uhlmann@cancer.org.uk

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