Dissecting mitotic chromosome condensation by high throughput DNA sequencing

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The faithful inheritance of genetic information is fundamental for ~~a~~ cell proliferation. Genetic information is stored as a long chain-like molecule, DNA, in the nucleus. To pack a metre-long DNA chain in micrometre-cubic nuclear space, DNA takes on the shape of a chromatin fibre. Chromatin architecture changes dramatically during the cell cycle. In interphase, chromatin is evenly distributed in the nucleus. Upon entry into mitosis, chromatin fibres become compacted and form condensed chromosomes, typically observed as X-shaped chromosome structures in higher eukaryotes. This process, called chromosome condensation, was first observed by W. Flemming in the late 19th century. It has attracted many scientists ever since, but its molecular mechanism is still not understood. An important discovery in the field is the condensin complex, one of the structural maintenance of chromosomes complexes (known as SMC complexes). In the absence of the condensin complex, chromosome condensation is disrupted and chromosome segregation fails. Here I present a DNA sequencing-based 'chromosome conformation capture' approach to gain insight into mitotic chromosome architecture.

Since DNA sequences are unique over their length, we can specify which chromosomal loci are close in space by determining DNA sequences of the proximal loci, following their chemical crosslinking. Using fission yeast as our initial model, our approach provides complete information on the spatial organisation of chromatin fibres within the nucleus in interphase and in condensed chromosomes in mitosis. We discovered that mitotic chromosome condensation is the consequence of increased intrachromosomal long-range interactions in the 150 - 200 kb distance range, promoted by the condensin complex. Using genetic approaches, we show that condensin acts by engaging in interactions between its chromosomal binding sites. Intriguingly, the increase in long-range interactions is accompanied by a loss of local chromatin interactions, with profound implications for chromatin function and gene expression. Our results shed light on the molecular mechanism how cells pack long chain-like chromatin fibres into small nuclear space and how condensed chromosomes are spatially organized through the activity of the condensin complex.