Nature Reviews Molecular Cell Biology | AOP, published online 14 September 2011; doi:10.1038/nrm3194

CELL CYCLE

The division belt

“chromosomes align into an equatorial ring”

The ability to visualize chromosome movements during cell division with unprecedented accuracy reveals a new feature of chromosome alignment during prometaphase. In *Cell*, two studies report that, in both mitosis and meiosis I, chromosomes align into an equatorial ring prior to bi-orientation — the configuration required for chromosome separation, in which kinetochores are stably attached to microtubules from the opposite poles of the spindle — and that the ring arrangement facilitates spindle assembly.

Khodjakov and colleagues made three-dimensional (3D) time-lapse movies of human cells undergoing mitosis and expressing green fluorescent protein (GFP) fused to proteins that localize to centrosomes and kinetochores. They observed that, during the initial stages of spindle formation, shortly after the nuclear envelope breaks down, chromosomes arrange into a ring around the spindle, with centromeres pointing inwards towards the spindle axis and arms pointing outwards. They also found that microtubules densely accumulate in the central part of the spindle and that centromeres are at the boundary of the spindle, with their kinetochores interacting with microtubules in a lateral manner. At later stages of spindle formation, chromosomes move to the central part of the spindle and form a typical metaphase plate, which precedes sister chromatid segregation in anaphase.

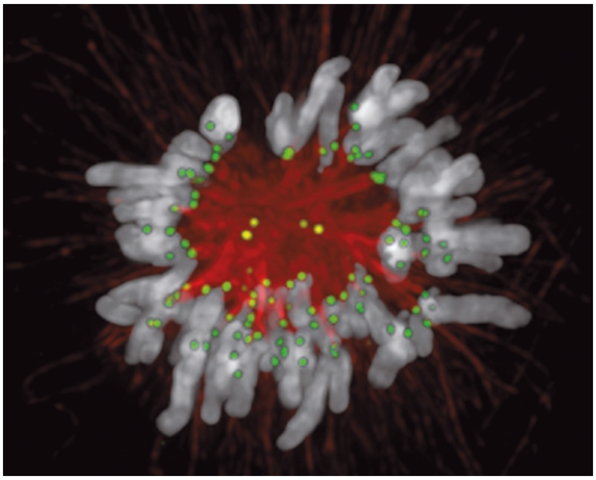
Next, the authors investigated the functional significance of these observations by using a computational model. This model predicted that the formation of the ring at the onset of mitosis facilitates the subsequent stable attachment of microtubule plus ends to kinetochores and accelerates assembly of the spindle by ~6–8 min. This prediction was confirmed experimentally: spindle formation was delayed when the formation of the ring was perturbed. Interestingly, the lateral interactions between kinetochores and microtubules that occur during chromosome ring formation were found to be sufficient to position chromosomes at the spindle equator. It is commonly thought that spindle assembly depends on the stable end-on microtubule attachment to kinetochores. However, tracking the movements of individual kinetochores in mutant cells in which these stable attachments did not form revealed, unexpectedly, that centromeres behave in a fairly normal manner during early stages of spindle formation. This indicates that kinetochore-based stabilization of the microtubules is a relatively late event in spindle formation.

In another study, Ellenberg and colleagues performed 3D live-cell imaging of meiosis I in mouse oocytes expressing GFP fused to kinetochore proteins. Unlike other cells, mammalian oocytes lack centrosomes. Therefore, the formation of a bipolar spindle is complex — upon nuclear envelope breakdown, many scattered microtubule-organizing centres reorganize to form a barrel-shaped spindle. How homologous chromosome bi-orientation is achieved and coordinated with such a complex spindle assembly mechanism is unknown.

By following chromosome dynamics during the first meiotic division, the authors observed that chromosomes form an intermediate configuration — the prometaphase belt. Chromosomes first arrange as a spherical shell around microtubules and then congress and become progressively ordered to form a ring structure in the equatorial region surrounding microtubules, a similar event to that observed by Khodjakov’s group during mitosis. Subsequently, chromosomes invade the elongating spindle centre, form the metaphase plate and become bi-oriented. Furthermore, the process of bi-orientation was shown to be highly error prone in oocytes: for each chromosome it requires multiple attempts, in which kinetochore attachments are lost and corrected several times in an Aurora B kinase-dependent manner. This finding is especially interesting in the light of the high incidence of aneuploidies of mammalian oocytes, which mostly arise in the meiosis I.

Together, these studies reveal previously unobserved features of chromosome spindle alignment. They both report the formation of a prometaphase chromosome ring, which may be a universal feature required for chromosome congression.

Kim Baumann



Mitotic spindle viewed along the spindle axis during early prometaphase. Microtubules (red) organized by the centrosomes (yellow) fill the centre of the spindle while chromosomes uniformly orient with the kinetochores (green) on the surface of the spindle and chromosome arms (white) pointing outwards. Image courtesy of C. O’Connell (Khodjakov laboratory), Wadsworth Center, New York, USA.

ORIGINAL RESEARCH PAPERS Magidson, V. *et al.* The spatial arrangement of chromosomes during prometaphase facilitates spindle assembly. *Cell* **146**, 555–567 (2011) | Kitajima, T. S., Ohsugi, M. & Ellenberg, J. Complete kinetochore tracking reveals error-prone homologous chromosome biorientation in mammalian oocytes. *Cell* **146**, 568–581 (2011)