Chromosome segregation during female meiosis in C. elegans: A tale of pushing and pulling

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The role of the kinetochore during meiotic chromosome segregation in C. elegans oocytes has been a matter of controversy. Danlasky et al. (2020. J. Cell. Biol. https://doi.org/10.1083/jcb.202005179) show that kinetochore proteins KNL-1 and KNL-3 are required for early stages of anaphase during female meiosis, suggesting a new kinetochore-based model of chromosome segregation.

Meiosis consists of two consecutive chromosome segregation events preceded by a single round of DNA replication. Homologous chromosomes are separated in meiosis I, which is followed by sister chromatid separation in meiosis II to produce haploid gametes. Both of these stages require chromosomes/chromatids to align during metaphase before separating to opposite poles during anaphase. During mitosis, microtubules emanating from centrosomes at opposite poles of the cell bind chromosomes through a multiprotein complex called the kinetochore, allowing chromosomes to be pulled apart (1, 2). This segregation event takes place in two stages: anaphase A, where chromosomes are pulled toward spindle poles due to microtubule depolymerization, and anaphase B, where spindle poles themselves move farther apart, taking the attached chromosomes with them (3, 4). In many organisms, including mammals, oocytes lack centrosomes, and it has been of great interest to clarify the mechanisms used to ensure chromosomes are properly segregated during female meiosis (5, 6). Caenorhabditis elegans has served as a model for studying both mitosis and meiosis, but microtubules between the separating chromosomes are (8), this model is unlikely, at least as an explanation for mid-/late-anaphase movement. Furthermore, although lateral microtubule interactions with chromosomes predominate during metaphase of C. elegans oocyte meiosis, cryo-electron tomography data described end-on attachments between the separating chromosomes as anaphase progresses (11). This led to the suggestion that lateral microtubule interactions with chromosomes are responsible for the initial separation, but microtubule polymerization between the separating chromosomes is required for the later stages of segregation (11).

The mechanisms involved in this initial separation have remained obscure. In this issue, Danlasky et al. show that the kinetochore is in fact required for the initial stages of chromosome segregation during female meiosis—an important step forward in our understanding of the mechanisms governing acentrosomal chromosome segregation (12). By simultaneously depleting kinetochore proteins KNL-1 and KNL-3 in C. elegans, Danlasky et al. observed the meiotic chromosome conformation and alignment defects described in previous studies (7). However, this double-depletion phenotype displayed three key characteristics: first, a role for kinetochores in chromosome segregation, which are discussed below.

The kinetochore is required for bivalent stretching. It was previously shown that the bivalent chromosomes stretch before the initiation of segregation (10).
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Danlasyk et al. found that this stretching of the chromosomes did not occur when KNL-1,3 were depleted, indicating that the kinetochore is required for this process (Fig. 1). Together with the observation that kinetochore proteins appear to extend toward the spindle poles, this finding suggested that pulling forces resulting from the interaction between the kinetochore and spindle microtubules are occurring during metaphase/pre-anaphase (Fig. 1).

The kinetochore is required for anaphase A. In C. elegans female meiosis, anaphase A occurs when homologous chromosomes begin to separate during spindle shortening, and anaphase B when the chromosomes separate alongside the spindle poles (10). Danlasyk et al. observed that KNL-1,3 depletion drastically reduced the velocity of anaphase A, as chromosomes only separated when spindle poles began to move apart. This indicated that pulling forces caused by the interaction between the kinetochore and spindle microtubules are also important for the initial separation of homologous chromosomes in anaphase A.

The kinetochore is required for proper separation of homologous chromosomes. In KNL-1,3 depletion strains, 60% of bivalents failed to separate before segregation began, resulting in intact bivalents being pulled to the same spindle pole (Fig. 1). This failure of homologous chromosomes to separate was not thought to be a result of KNL-1,3 depletion interfering with the cleavage of cohesin that holds the two homologous chromosomes together because (a) separase and AIR-2\textsuperscript{AuroraB}, both of which are required for cohesin cleavage, localized normally during metaphase and anaphase, and (b) bivalents separated by metaphase II. This leaves the possibility open that the failure of bivalents to separate was due to the disrupted pulling forces thought to be important in bivalent stretching and anaphase A.

Altogether, these data strongly indicate that the kinetochore is required not only for chromosome congression and alignment but also for the early stages of homologue separation. Anaphase B occurred successfully in the absence of KNL-1,3 but was more error prone, likely as a result of the earlier congression and anaphase A defects. While it is clear that chromosome masses do segregate in the absence of the kinetochore, this segregation is highly erroneous as a result of defects during the earlier stages of segregation in anaphase A (Fig. 1).

The findings of Danlasyk et al. raise testable hypotheses that could significantly enhance our understanding of acentrosomal chromosome segregation. Further investigation of the proposed pulling forces required during metaphase and early anaphase will be of great interest. Additionally, a more detailed analysis of the dynamic localization of separase and Securin, as well as assessing successful cohesin cleavage when KNL-1,3 are depleted, would back up the assertion that the failure of homologous chromosomes to separate was not due to the kinetochore impacting cohesin cleavage. It has previously been shown that the CLASP orthologue CLS-2 in C. elegans localizes to the kinetochore surrounding the bivalent chromosomes during metaphase before relocating to the central spindle during anaphase (7, 8, 13).

While the regulation of proper chromosome segregation during acentrosomal meiosis in C. elegans is not yet fully understood, Danlasyk et al.’s results represent a significant step forward in this endeavor by showing that the kinetochore is in fact required for the early stages of chromosome segregation.

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