Better safe than sorry—preventing mitotic segregation of meiotic chromosomes

Régis E. Meyer and Dean S. Dawson

Program in Cell Cycle and Cancer Biology, Oklahoma Medical Research Foundation, Oklahoma City, Oklahoma 73104, USA

The distinctive segregation patterns of chromosomes in mitosis and meiosis are dictated in part by the kinetochores, the structures on chromosomes that attach them to the microtubules of the spindle. Inappropriate mitosis-like chromosome segregation in meiosis leads to gametes with incorrect chromosome numbers. New findings by Chen and colleagues (pp. 209–225) in this issue of *Genes & Development* reveal how cells restructure their kinetochores when they enter meiosis. Their results describe an interconnected set of mechanisms that provides multiple layers of protection from the carryover of mitotic chromosome segregation patterns into meiotic cells.

Mitosis and meiosis are both designed to segregate chromosomes away from their partners, but the partners are different (Fig. 1A). In mitosis, sister chromatids segregate to opposite poles of the spindle. In contrast, in the first meiotic division, it is homologous chromosomes that segregate, while the centromeres of sister chromatids remain together until they separate in meiosis II. The abnormal segregation of chromosomes in a mitosis-like pattern in meiosis results in gametes with incorrect chromosome numbers, which in turn leads to aneuploid progeny (Fig. 1B). To avoid this costly error, cells that are entering meiosis must be reprogrammed, because in prior divisions they segregated their chromosomes in a mitotic pattern.

How is this accomplished? Chen et al. (2020) build on their prior studies, as well as work from other laboratories, to illuminate a collection of mechanisms that provides layers of protection against mitotic-like chromosome segregation behavior occurring in meiosis. In yeast cells going through mitotic cycles, the chromosomes are attached almost constantly via their kinetochores (structures composed of >60 proteins that reside at the centromeres) to microtubules that emanate from the microtubule-organizing centers (called spindle pole bodies in yeast) (Fig. 1A). The kinetochores only release the microtubules briefly when the chromosomes are being replicated. When S phase is complete, the replicated sister chromatids are tethered together by cohesins and are immediately ready to segregate on a newly formed spindle.

Meiosis is a different story; here, chromosomes are not at all ready for segregation after DNA replication is complete. Instead, the pairs of sister chromatids must identify their homologous partners, pair with their homolog, and become tethered by chiasmata. This all occurs during a lengthy meiotic prophase (Fig. 1A). As cells exit meiotic prophase, they add meiosis-specific proteins (monopolins in budding yeast) (Tóth et al. 2000) to the sister chromatid kinetochores. This allows the sister kinetochores to share a single attachment point for microtubules. If the sister chromatids were to become connected to microtubules and begin segregating in prophase, before homologous chromosomes became tethered, then sister chromatids —not homologous partners—could separate in the first meiotic division. This catastrophic outcome is prevented by a collection of fail-safe mechanisms.

As a first line of defense in meiotic cells, Ipl1 (Aurora B) kinase, which plays key roles in mitotic regulation, blocks meiotic spindle formation during prophase (Fig. 1A; Shirk et al. 2011; Kim et al. 2013). This reduces the chance that sister chromatids will interact precociously with microtubules that could begin segregating them prematurely. As a second line of defense, expression of the outer kinetochore *NDC80* gene is diminished in meiotic prophase and only turns on after homolog partners are paired (Brar et al. 2012; Miller et al. 2012). Ndc80 is part of a four-protein subcomplex (the NDC80 complex) at the outer kinetochore. The Ndc80 protein itself is the component of the kinetochore that directly connects to the microtubule (Fig. 1C). This repression is accomplished via a newly discovered meiotic transcriptional regulatory mechanism. In prophase, a long undecoded transcript isoform (LUTI) of the *NDC80* gene is expressed. This *NDC80*^{LUTI} transcript interferes with the expression of the canonical *NDC80* transcript (Chen et al. 2017; Cheng et al. 2018).

[*Keywords*: meiosis; kinetochore; Aurora B; Ndc80; chromosome; proteolysis; APC]
Corresponding author: dawsond@omrf.org
Article is online at http://www.genesdev.org/cgi/doi/10.1101/gad.336164.119.

© 2020 Meyer and Dawson This article is distributed exclusively by Cold Spring Harbor Laboratory Press for the first six months after the full-issue publication date (see http://genesdev.cshlp.org/site/misc/terms.xhtml). After six months, it is available under a Creative Commons License (Attribution-NonCommercial 4.0 International), as described at http://creativecommons.org/licenses/by-nc/4.0/.

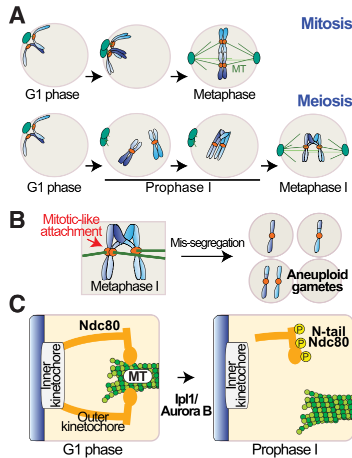

Figure 1. Kinetochore behavior in meiosis. (*A*) Chromosome segregation patterns in mitosis and meiosis I. Meiotic cells feature an extended prophase to allow homologous partners to become joined by chiasmata. (*B*) Inappropriate mitotic-like segregation of sister chromatids in meiosis I. (*C*) Phosphorylation of Ndc80 by Aurora B kinase promotes restructuring of kinetochores in meiosis.

What of the Ndc80 protein that is present on the kinetochores when cells enter meiosis? The Ndc80 complex is removed from kinetochores when cells enter meiosis by a mechanism that requires Ipl1, and levels of Ndc80 are sharply reduced when cells enter meiosis (Asakawa et al. 2005; Meyer et al. 2013, 2015). Ectopic expression of Ndc80 in meiotic prophase causes chromosome missegregation (Miller et al. 2012; Chen et al. 2017), so this removal of Ndc80 is critical. The new work by Chen et al. (2020) reveals how the cell protects itself from missegregation by removing Ndc80 from kinetochores. First, they found that when cells enter meiotic prophase, the Ndc80 subunit is phosphorylated along its N terminus by Ipl1 (Fig. 1C). Interestingly, in many species, this conserved part of Ndc80 is critical for its binding to microtubules, and its phosphorylation by Aurora B allows Ndc80 to release inappropriate microtubule connections. Second, they found that phosphorylation of the Ndc80 N-terminal tail promotes the release of the kinetochores from microtubules as cells enter meiosis and the chromosomes begin identifying their homologous partners. Remarkably, as an added level of protection, Chen et al. (2020) discovered that, in meiosis, the phosphorylation of Ndc80 results in targeted degradation of Ndc80. This degradation is specific to meiotic prophase; when expressed in metaphase I, the Ndc80 protein is stable.

The degradation of the phosphorylated Ndc80 was shown to be dependent on the meiosis-specific anaphase-promoting complex (APC) activator Ama1. The APC ubiquitinates proteins, targeting them for proteolytic degradation. Reversing these protective measures is necessary to assemble a new meiotic kinetochore. When the homologous partners are tethered by chiasmata and ready to segregate, increasing cyclin-dependent kinase levels allow increased Ndc80 expression (use of the non-LUTI promoter) and increased Ndc80 stability (through reduced Ama1 activity). The rise in Ndc80 levels, concomitant with the expression of monopolin components, allows the assembly of new meiotic-specific outer kinetochores on the paired homologous partners.

Together, these studies illustrate that budding yeast has developed a quadruple safety system—preventing prophase spindle formation, reducing *NDC80* expression in prophase, shedding of Ndc80 from the prophase kinetochores, and degradation of Ndc80 phosphorylated in prophase—to prevent mitotic-like segregation of chromosomes meiosis I.

Acknowledgments

This work was supported by National Institutes of Health grant R01GM110271.

References

Asakawa H, Hayashi A, Haraguchi T, Hiraoka Y. 2005. Dissociation of the Nuf2–Ndc80 complex releases centromeres from the spindle-pole body during meiotic prophase in fission yeast. *Mol Biol Cell* **16:** 2325–2338. doi:10.1091/mbc.e04-11-0996

Brar GA, Yassour M, Friedman N, Regev A, Ingolia NT, Weissman JS. 2012. High-resolution view of the yeast meiotic program revealed by ribosome profiling. *Science* **335:** 552–557. doi:10.1126/science.1215110

Chen J, Tresenrider A, Chia M, McSwiggen DT, Spedale G, Jorgensen V, Liao H, van Werven FJ, Unal E. 2017. Kinetochore inactivation by expression of a repressive mRNA. *Elife* **6:** 823. doi:10.7554/eLife.27417

Chen J, Liao A, Powers N, Liao H, Kohlstaedt LA, Evans R, Holly RM, Kim JK, Jovanovic M, Ünal E. 2020. Aurora B-dependent Ndc80 degradation regulates kinetochore composition in meiosis. *Genes Dev* (this issue). doi:10.1101/gad.333997.119

Cheng Z, Otto GM, Powers EN, Keskin A, Mertins P, Carr SA, Jovanovic M, Brar GA. 2018. Pervasive, coordinated protein-level changes driven by transcript isoform switching during meiosis. *Cell* **172:** 910–923.e16. doi:10.1016/j.cell.2018.01.035

Kim S, Meyer R, Chuong H, Dawson DS. 2013. Dual mechanisms prevent premature chromosome segregation during meiosis. *Genes Dev* **27:** 2139–2146. doi:10.1101/gad.227454.113

Meyer RE, Kim S, Obeso D, Straight PD, Winey M, Dawson DS. 2013. Mps1 and Ipl1/Aurora B act sequentially to correctly orient chromosomes on the meiotic spindle of budding yeast. *Science* **339:** 1071–1074. doi:10.1126/science.1232518

Meyer RE, Chuong HH, Hild M, Hansen CL, Kinter M, Dawson DS. 2015. Ipl1/Aurora-B is necessary for kinetochore restructuring in meiosis I in *Saccharomyces cerevisiae*. *Mol Biol Cell* **26:** 2986–3000. doi:10.1091/mbc.E15-01-0032

Miller MP, Ünal E, Brar GA, Amon A. 2012. Meiosis I chromosome segregation is established through regulation of microtubule–kinetochore interactions. *Elife* **1:** e00117. doi:10.7554/eLife.00117

Shirk K, Jin H, Giddings TH, Winey M, Yu H-G. 2011. The Aurora kinase Ipl1 is necessary for spindle pole body cohesion during budding yeast meiosis. *J Cell Sci* **124:** 2891–2896. doi:10.1242/jcs.086652

Tóth A, Rabitsch KP, Gálová M, Schleiffer A, Buonomo SB, Nasmyth K. 2000. Functional genomics identifies monopolin: a kinetochore protein required for segregation of homologs during meiosis I. *Cell* **103:** 1155–1168. doi:10.1016/S0092-8674(00)00217-8