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SPOTLIGHT

CKS-1 and the choreography of meiotic chromosome segregation

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Meiotic progression requires the activity of the cyclin B–CDK1 complex. In this issue, Yang et al. (https://doi.org/10.1083/jcb.202502087) demonstrate that the phospho-adaptor protein CKS-1 functions as a critical component of this complex to ensure proper chromosome segregation during oocyte meiosis.

Meiosis partitions the genome through a sequence of highly choreographed events that set it apart from mitosis (1). It proceeds through two sequential chromosome segregation events that reduce the genome to form haploid gametes for sexual reproduction. This is achieved by separation of paired homologous chromosomes in meiosis I, followed by sister chromatid segregation in meiosis II (Fig. 1). These divisions must be precisely regulated, as errors can disrupt faithful genome transmission (1). Therefore, unraveling the molecular mechanisms controlling meiotic chromosome segregation is crucial for our understanding of fertility, genetic diversity, and the perpetuation of sexually reproducing species.

Both mitotic and meiotic cell divisions are driven by cyclin-dependent kinase-1 (CDK1), whose activity depends on binding by its partner cyclin B (2). In several systems, cyclin B exists as two essential isoforms known as cyclin B1 and cyclin B3 (2). In addition, the cyclin B–CDK1 complex interacts with a small protein known as cyclin-dependent kinase subunit (CKS) (3). CKS possesses an anion-binding pocket that recognizes phosphorylated threonine residues, functioning as a molecular tether that anchors the cyclin B–CDK1 complex onto prephosphorylated substrates. This tethering often triggers waves of additional CDK1-dependent phosphorylation events, amplifying the reach of the kinase (3, 4). In several systems, loss of CKS results in cell-cycle defects, particularly during anaphase, well after CDK1 has driven the cell to enter division (3, 5). Though CKS has been implicated in cell-cycle control, its role in meiosis is not fully understood.

In this study, Yang et al. investigate the function of CKS in female meiosis in *Caenorhabditis elegans* (6). Prior work had shown that knockdown of CKS-1, the sole CKS ortholog in *C. elegans*, results in a lack of polar body formation during oocyte meiosis (5), but the precise molecular pathway remained elusive. To address this topic, Yang et al. used elegant live fluorescence microscopy to image *in utero* and *ex utero* oocytes through sequential meiotic divisions. First, they took advantage of CRISPR-Cas9 technologies to generate *C. elegans* strains expressing CDK1 and CKS-1 endogenously tagged with fluorescent proteins. They found that CDK1 and CKS-1 persistently colocalize at meiotic structures, including kinetochore "cups," linear elements, and the central spindle, suggesting that CDK1 and CKS-1 form a tight complex throughout meiosis. To address the role of CKS-1 in meiosis, Yang et al. meticulously characterized CKS-1 functionality using multiple complementary inhibition approaches such as RNAi, CRISPR knockout lines, and the auxin-inducible degron (AID) system. Regardless of the approach, they found that CKS-1 inhibition resulted in a pronounced (~twofold) delay in the transition from metaphase I to anaphase I. It is well known that this transition depends on the timely degradation of two factors: cyclin B1 - the activator of CDK1; and securin - the inhibitor of separase whose activity triggers chromosome segregation (7). Thus, the authors examined their dynamics. Notably, they found that degradation of both proteins was significantly delayed in CKS-1–depleted oocytes. However, this delay was suppressed by codepletion of securin, but not cyclin B1. Securin degradation depends on the activity of the anaphase-promoting complex/cyclosome (APC/C), an E3 ubiquitin ligase (8). Additionally, CKS is required for the phosphorylation and, subsequently, activation of the APC/C (9). Thus, these findings are consistent with CKS-1 promoting the metaphase I–to–anaphase I transition through APC/C activation and, subsequently, securin degradation (Fig 1).

Strikingly, the authors found that when CKS-1–inhibited oocytes eventually progressed through metaphase I, chromosome segregation proceeded in an unexpected manner. Using a multitude of fluorescent markers for anaphase progression, the authors found that upon CKS-1 depletion, chromosomes initially separated in a manner that is consistent with anaphase A, which is driven by chromosomes migrating toward spindle poles as spindles shortened (10). However, anaphase B, which relies on spindle microtubules repositioning between separating homologs to drive them apart (10), failed completely in CKS-1's absence. These findings are in line with the notion that chromosome movement during anaphase A and spindle elongation during anaphase B can be differentially regulated during oocyte meiosis (11). Thus, this work

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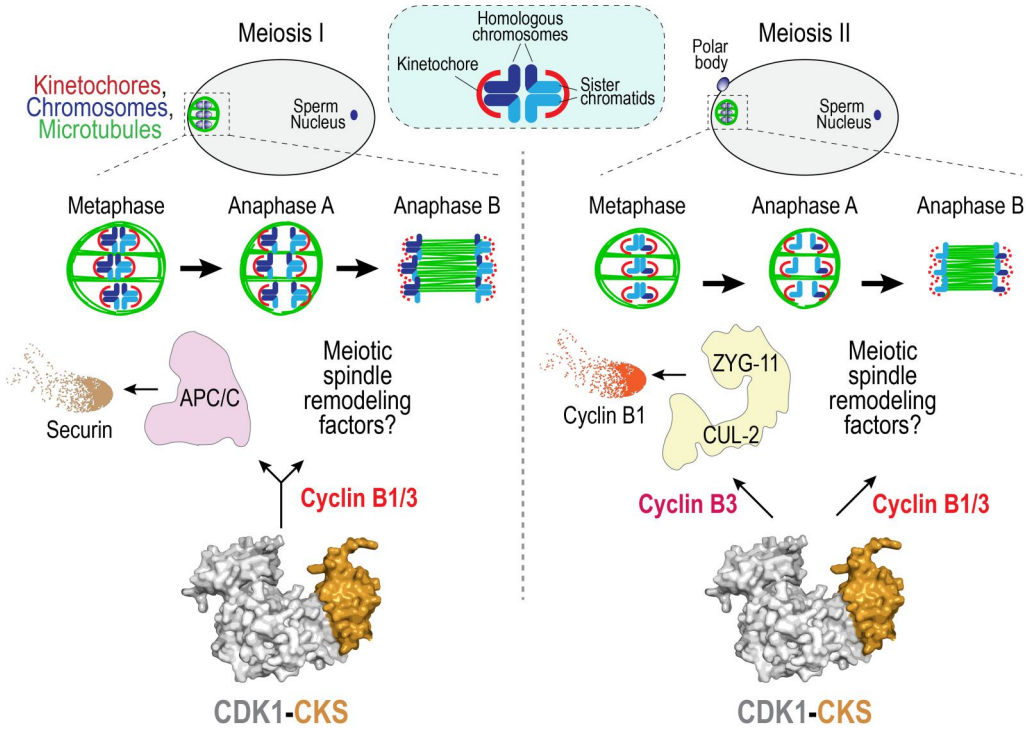

Figure 1. **CKS ensures proper meiotic chromosome segregation.** During meiosis I, the CDK1–CKS complex works with cyclins B1 and B3 to promote activation of the APC/C, which in turn degrades securin to ensure the metaphase-to-anaphase transition. During meiosis II, the cyclin B3–CDK1–CKS complex promotes the metaphase-to-anaphase transition by positively regulating the ZYG-11/CUL-2 ubiquitin ligase to target cyclin B1 for degradation. During both meiotic divisions, the cyclin B1/3–CDK1–CKS complex promotes anaphase B chromosome segregation via an unknown mechanism that likely involves meiotic spindle remodeling factors. The CDK1–CKS cartoon is based on an AlphaFold3 model of the predicted *C. elegans* complex.

revealed a previously unappreciated role for CKS-1 in coordinating chromosome segregation during meiosis I.

Having convincingly demonstrated that CKS-1 is crucial for meiosis I chromosome segregation, the authors next asked: Does CKS also function during meiosis II? Because depletion of CKS precludes chromosome segregation in meiosis I, investigating its subsequent roles required a strategic approach. To tackle this challenge, the authors elegantly used the AID system to acutely deplete CKS-1 at the meiosis I/meiosis II transition. Using this system, they found that CKS-1 depletion also delayed the metaphase II–to–anaphase II transition. However, interestingly, this delay depended on the presence of cyclin B1, but not securin. The authors interpreted these results to indicate that CKS-1 promotes anaphase onset by ensuring securin degradation during meiosis I, while facilitating cyclin B1 degradation during meiosis II. Prior work had shown that cyclin B degradation during meiosis II depended on the CUL-2/ZYG-11 ubiquitin ligase, which functions in parallel to APC/C-mediated degradation (2). Using epistasis analyses, the authors found that CKS-1 depletion did not enhance the meiosis II delay caused by ZYG-11 depletion, thus supporting a model in which CKS-1 promotes meiosis II chromosome segregation by working with the CUL-2/ZYG-11 ubiquitin ligase (Fig. 1). This function likely also requires the specific activation of CDK1 by cyclin B3, as cyclin B3 depletion also delayed metaphase II and cyclin B1 degradation.

Taken together, these findings revealed that CKS, through its ability to tether cyclin B–CDK1 to phosphorylated substrates, functions at multiple levels to drive meiotic chromosome segregation. Yet, these findings open the door to several unanswered questions that may reshape our understanding of meiotic cell division. First, how does the cyclin B–CDK1–CKS complex selectively promote anaphase B chromosome segregation? As mentioned above, anaphase B involves a dramatic spindle remodeling event where it transforms from a barrel-shaped structure that encapsulates meiotic chromosomes into a dynamic apparatus that forms between bivalent chromosomes to push them apart (11). One possibility is that CKS drives hyperphosphorylation and activation of key anaphase B spindle remodeling factors such as CLS-2 or ZYG-8 (11, 12). Unraveling the molecular mechanism by which CKS drives anaphase B would require approaches such as phospho-mass spectrometry analyses for substrate identification; however, the brief temporal window of meiotic chromosome segregation makes such experiments challenging. An alternative approach would involve mutational screens targeting putative phosphorylation sites on proteins involved in anaphase B for the identification of direct targets of cyclin B–CDK1–CKS complexes in meiosis. A second question is: How does CKS promote ZYG-11/CUL-2 activity? Prior work had shown that CKS proteins enhance cyclin B1 degradation in mitosis either by driving APC/C hyperphosphorylation or by tethering the cyclin B1-CDK1 complex to phosphorylated APC/C (8). However, how CKS promotes activation of CUL-2/ZYG-11 remains unexplored. The authors speculate that cyclin B3–CDK1–CKS promotes phosphorylation of the ZYG-11 adaptor protein to enable cyclin B1 recognition, but the precise molecular mechanism remains elusive.

Overall, this work has delivered valuable insights into how the cyclin B–CDK1–CKS complex ensures meiotic chromosome segregation, which will likely set the stage for future discoveries in this fundamental biological process.

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