

Targeting Polo-like kinase in space and time during *C. elegans* meiosis

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ABSTRACT

A central player in meiotic chromosome dynamics is the conserved Polo-like kinase (PLK) family. PLKs are dynamically localized to distinct structures during meiotic prophase and phosphorylate a diverse group of substrates to control homolog pairing, synapsis, and meiotic recombination. In a recent study, we uncovered the mechanisms that control the targeting of a meiosis-specific PLK-2 in *C. elegans*. In early meiotic prophase, PLK-2 localizes to special chromosome regions known as pairing centers and drives homolog pairing and synapsis. PLK-2 then relocates to the synaptonemal complex (SC) after crossover designation and mediates chromosome remodeling required for homolog separation. What controls this intricate targeting of PLK-2 in space and time? We discuss recent findings and remaining questions for the future.

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Meiosis proceeds through stepwise chromosome rearrangement

Sexually reproducing organisms rely on the correct execution of meiosis, a specialized cell division that produces haploid gametes such as sperm and eggs. The reduction in chromosome number during meiosis is achieved by a single round of DNA replication, followed by two consecutive nuclear divisions. Unique to meiosis is the protracted prophase, in which chromosomes pair and synapse with their homologous partners through the formation of a zipper-like protein scaffold called the synaptonemal complex (SC) [1,2]. Concomitant with pairing and synapsis, meiotic recombination initiates with induction of programmed DNA double-strand breaks (DSBs) [3]. A subset of these breaks is eventually processed to form crossovers [4], which physically link each pair of homologs and enable their proper separation during meiosis I. This process also allows for new combinations of alleles, thereby promoting genetic variation that underlies eukaryotic evolution.

Polo-like kinases coordinate meiotic chromosome dynamics

During meiosis, as in mitosis, PLKs regulate many aspects of cell cycle events that are essential for

successful chromosome segregation. The sole PLK in budding yeast, Cdc5, is required for crossover formation and SC disassembly, thereby permitting cells to exit pachytene [5,6]. The Polo kinase in fission yeast, Plo1, is excluded from the spindle pole body (SPB) during meiotic prophase [7,8], although the significance of SPB remodeling on telomere-led “horsetail” movement and homolog pairing remains to be determined. In *Drosophila* and mouse oocytes, prolonged meiotic arrest requires the inhibition of PLK1 [9,10], consistent with its conserved role in prophase exit [11,12]. While the *Drosophila* Polo is not detected in oocytes until the very late stage of meiotic prophase [10], mammalian PLK1 localizes to the SC in pachytene and promotes its disassembly [13]. During meiosis I, PLKs are recruited to kinetochores through meiosis-specific adaptors (mouse Meikin, budding yeast Spo13, and fission yeast Moa1) and play critical roles in mono-orientation of sister kinetochores and sister chromatid cohesion [5,14–17]. Interestingly, the catalytically active form of *Drosophila* Polo is sequestered away from chromosomes during female meiosis I by a meiosis-specific protein, Matrimony, and inhibiting the Polo activity at centromeres is essential for protecting cohesion during meiosis I [10,18]. Thus, although the details may vary

depending on the organism, PLKs play universally important roles in coordinating the complex behavior of meiotic chromosomes.

PLK-2 is a meiosis-specific paralog of PLK-1 in *C. elegans*

Perhaps the most pervasive role for PLK has been demonstrated during *C. elegans* meiosis, in which meiosis-specific PLK-2 regulates homolog pairing, synapsis, programmed DSB formation, and chromosome remodeling that defines the pattern of cohesin release during meiotic divisions [19–23]. PLK-2 is one of three PLK orthologs in *C. elegans* that are closely related to the mammalian PLK1 [24]. In a phylogenetic analysis, PLK-1, PLK-2, and PLK-3 are grouped together with PLK1 orthologs, rather than members of the vertebrate PLK2 subfamily (Figure 1), suggesting that PLK-2 and PLK-3 arose from gene duplication events in nematodes. While the function of PLK-3 is unknown, PLK-1 and PLK-2 play redundant roles in establishing the cell polarity in embryos [25]. PLK-1 can also localize to pairing centers and partially substitute for PLK-2's function to promote homolog pairing and synapsis [19,20],

corroborating that PLK-2 is a meiosis-specific paralog of PLK-1.

Two PLK-2 docking sites are generated by distinct priming kinases

To ensure that PLK-2 coordinates distinct meiotic events at the right space and time, multiple layers of control are in place to direct PLK-2 to specific subcellular locations during meiotic progression. Localization of PLKs is largely governed by their Polo-box domain (PBD), which binds a phosphorylated protein motif (S-[pS/T]-P/X) [26,27]. Thus, “priming” these motifs by phosphorylation provides an initial layer of control for targeting PLKs. In *C. elegans*, a meiosis-specific Ser/Thr kinase, CHK-2, primes the recruitment of PLK-2 to pairing centers by phosphorylating a family of zinc finger proteins (HIM-8, ZIM-1, ZIM-2, and ZIM-3) [28] that bind specific DNA sequence motifs enriched at pairing centers [29,30]. Recent work has shown that another PBD-docking site is present within an SC component, SYP-1 [31], which is phosphorylated by the cyclin-dependent kinase, CDK-1, just before meiotic onset [32]. Thus, two major PBD-

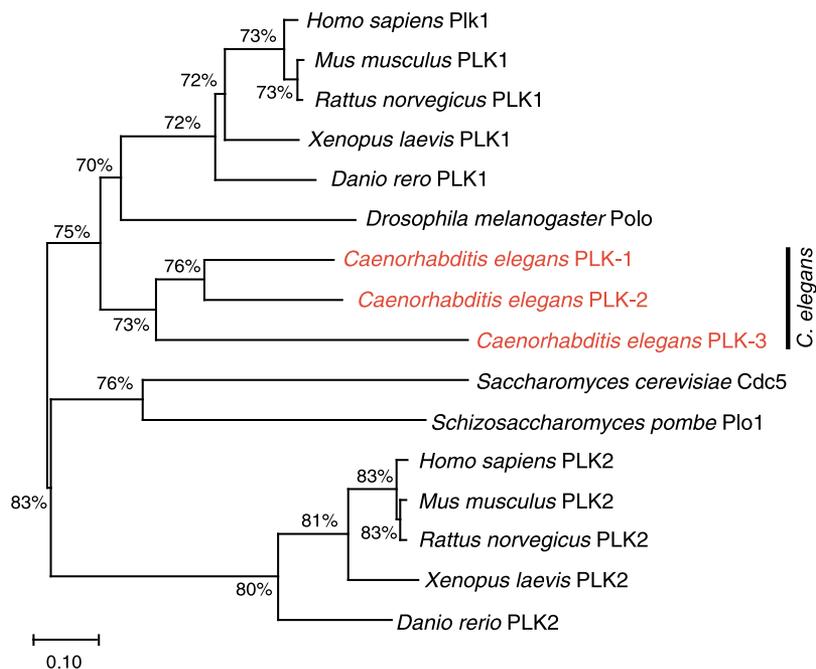


Figure 1. Phylogenetic tree of members of the Polo-like kinase family.

The analysis was performed using the Neighbor-joining method and Poisson correction model in MEGA X [57]. Scale bar indicates the number of substitutions per site. Bootstrap values are displayed on each node

binding sites are generated in early meiotic prophase (Figure 2a), each primed by CDK-1 and CHK-2 that are essential for mitotic and meiotic cell cycle progression, respectively.

PLK-2 is preferentially targeted to pairing centers by nucleoplasmic regulation

Interestingly, of the two PLK-docking sites, PLK-2 is preferentially targeted to pairing centers in early meiotic prophase where it acts locally to drive homolog pairing and synapsis. The SC is capable of recruiting PLK-2 only when the four pairing center proteins (HIM-8, ZIM-1, ZIM-2, and ZIM-3) are absent at this stage of meiosis [19,32,33]. How do pairing centers win over this competition and recruit PLK-2 at the onset of meiosis? An insight into this problem came from

the identification of the nucleoplasmic protein complex consisting of HAL-2 and HAL-3, which functions to promote full activation of CHK-2 and to antagonize PLK-2 activity in the nucleoplasm [33,34]. Mutations in *hal-2* or *hal-3* result in the displacement of PLK-2 from the pairing center into the nucleoplasm, despite residual CHK-2 activity in the nucleus, and the unleashed PLK-2 activity in the nucleoplasm leads to inappropriate phosphorylation of PLK-2 substrates and defects in axis assembly, homolog pairing, and synapsis [33,34]. Remarkably, these phenotypes in *hal-2* mutants can be rescued by mutating the PBD-binding motif on SYP-1 [32], revealing that a key function of the HAL-2/3 complex is to prevent precocious association between PLK-2 and the SC in early prophase (Figure 2a). Thus, PLK-2 is sequestered to the pairing centers through an

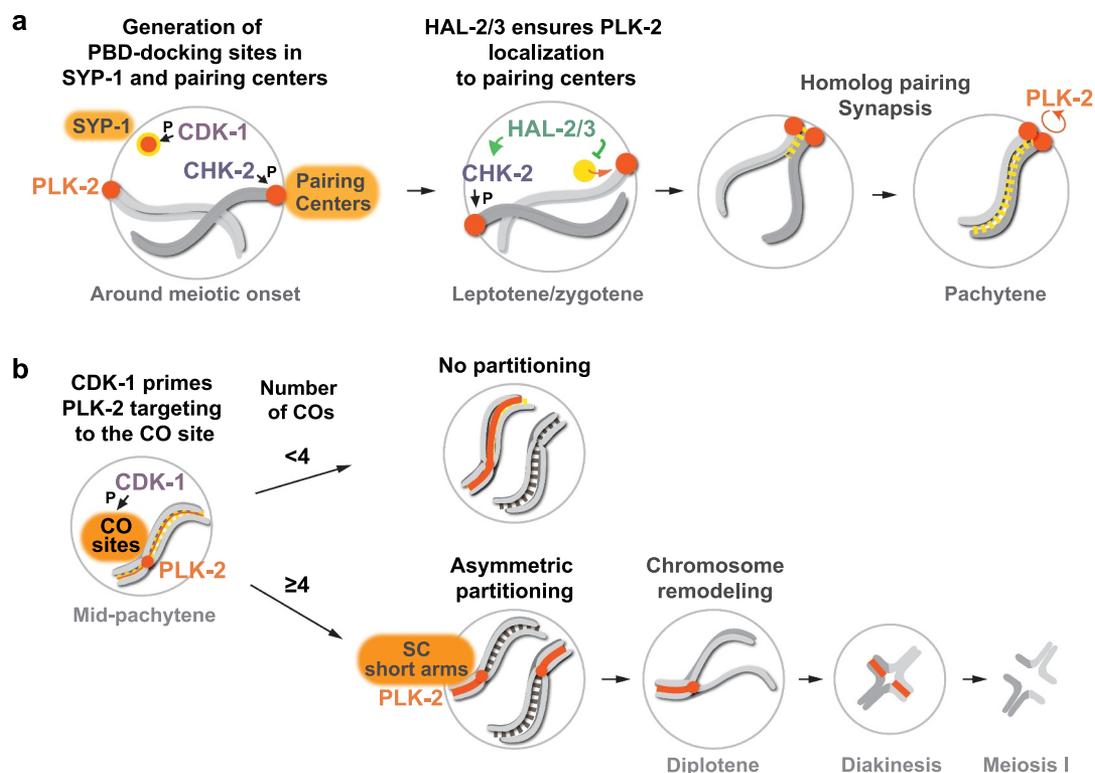


Figure 2. Multiple layers of control to regulate dynamic PLK-2 localization during meiotic prophase in *C. elegans*.

(A) Schematic illustrating the mechanism that controls the preferential targeting of PLK-2 to pairing centers in early meiotic prophase. (B) PLK-2 is first recruited to the crossover site, which is primed by CDK-1. The asymmetric enrichment of PLK-2 to the SC short arm requires its own kinase activity and depends on the number of crossover-designated sites within the nucleus

active mechanism that involves HAL-2/3, and this is critical for proper homolog pairing and synapsis.

This role of HAL-2/3 is analogous to the function of Matrimony in *Drosophila* female meiosis. Matrimony was initially discovered as a gene that is haplo-insufficient for achiasmate segregation in *Drosophila* oocytes [35] and was later shown to be a negative regulator of Polo kinase [10]. Matrimony directly binds Polo and limits its activity on chromosomes by sequestering the catalytically active Polo kinase to the microtubule spindle during meiosis I [10,18,36]. Loss of Matrimony leads to precocious loss of sister chromatid cohesion, and this can be rescued by lowering Polo kinase activity [10,18]. Similarly, defects in synapsis and meiotic recombination in *hal-3* mutants are partially rescued by the null mutation of *plk-2* [33], demonstrating that spatial regulation of PLK activity is essential for a successful outcome of meiosis in both *Drosophila* and *C. elegans*. HAL-2 and HAL-3 are not conserved outside of the *Caenorhabditis* species and share similar characteristics to a rapidly evolving group of meiosis-specific proteins that regulate key cell cycle kinases [37]. However, unlike Matrimony, HAL-2 and HAL-3 do not possess PBD-docking motifs or domains with recognizable functions. Thus, it remains mysterious how the HAL-2/3 complex functions to regulate the interaction between PLK-2 and SYP-1. It is worth noting that, although HAL-2 and HAL-3 are largely found in the nucleoplasm during normal meiosis, they colocalize with SC aggregates known as “polycomplexes” in the absence of chromosome axes [34]. Thus, the HAL-2/3 complex appears to have an affinity to the SC and is likely to act on the soluble pool of SYP proteins before their loading onto chromosomes. Future work will be necessary to determine how HAL-2 and HAL-3 regulate CHK-2 activity and PLK-2's association with the SC.

Recruitment of PLK-2 to the SC requires crossover formation and a self-reinforcing mechanism

While the PBD-docking motifs within HIM-8/ZIMs are dephosphorylated as CHK-2 activity is weakened after chromosomes pair and synapse [28], SYP-1 phosphorylation by CDK-1 persists

along the length of chromosomes throughout pachytene [31,32]. However, PLK-2 is unable to relocate to the SC in late pachytene, unless crossover designation occurs [32]. Thus, the priming phosphorylation of SYP-1 by CDK-1 is not sufficient for the spatiotemporal control to recruit PLK-2 to the SC. What prevents the stable association between PLK-2 and the SC prior to crossover formation is currently unknown. In our analysis, a kinase-dead mutant of PLK-2 precociously spreads to the SC in early pachytene [32], indicating that PLK-2 activity is necessary for maintaining its tight association with pairing centers (Figure 2a). It is possible that the rapid, dynein-driven motion of pairing centers, sustained by the concentrated PLK-2 activity at the pairing center [19,20,38–40], serves as a thermodynamic barrier that must be overcome before PLK-2 can access its binding sites on SYP-1. As the inactivation of CHK-2 and cessation of pairing center movement are coupled to SC assembly and crossover formation [28,41–43], this feedback mechanism may help license the PLK-2 recruitment to the SC upon crossover formation.

Then, how does the crossover event transmit signals across the length of chromosomes to recruit PLK-2 to the SC? Recent cytological analysis of recombination sites in *C. elegans* has revealed that PLK-2 colocalizes with pro-crossover proteins within the SC “bubble” [44]. Consistent with this finding, our evidence suggests that PLK-2 is first recruited to crossover sites in a CDK-1-dependent manner before spreading along the SC (Figure 2b) [32]. It remains to be determined which proteins at the crossover site are phosphorylated by CDK-1 to generate docking sites for PLK-2. In budding yeast, Cdc5 is recruited to the crossover site through a direct binding to Exo1 and is important for MutL-mediated crossover resolution [45]. Thus, localization of PLK to crossover-designated recombination intermediates might be a conserved feature of crossover regulation, and potential functions for PLK-2 at the crossover site will be an important avenue for future research.

Earlier evidence has shown that crossover-designated sites transmit a signal to enrich for PLK-2 and stabilize the SC *in cis* [21–23]. This change in the dynamic state of the SC has been

shown to depend on PLK-2 [21–23], which retains SYP-1 phosphorylation on chromosomes harboring crossovers using its own kinase activity [32]. How PLK-2 reinforces its own docking sites and spreads from the crossover site to the SC is currently unclear. Although a self-priming and binding mechanism for PLK can promote its own localization [27], PLK-2 was unable to phosphorylate the PBD-docking motif on SYP-1 in our in vitro kinase assays [32]. Thus, we favor a scenario where PLK-2 activity indirectly supports the retention of phosphorylated SYP-1 by affecting the SC turnover and/or locally modulating CDK-1 activity.

PLK-2 localization is responsive to both nucleus-wide and chromosome-autonomous signaling

In holocentric *C. elegans*, which lacks defined centromeres [46], a single crossover event partitions the chromosome into two distinct domains (long and short arms) and defines where cohesion will be released during meiosis I (Figure 2b) [47–53]. However, it remains poorly understood how the presence of crossovers is signaled to partition meiotic chromosomes. One of the earliest events that differentiate the long versus short arm is the recruitment of PLK-2 to the SC short arm, which mediates axis remodeling and asymmetric SC disassembly [19,21,31]. Intriguingly, this asymmetric appearance of PLK-2 and SYP-1 phosphorylation depends on the number of crossover-designated sites within each nucleus [32], suggesting that the symmetry breaking of bivalent chromosomes is controlled by nucleus-wide signaling. In nuclei with low numbers of crossovers (<4), no partitioning occurs, and PLK-2 localizes along the entire length of chromosomes that have designated crossovers, while it is lost from chromosomes without crossovers. However, in nuclei with higher number of crossovers (≥ 4), PLK-2 and SYP-1 phosphorylation exhibit the asymmetric localization on the SC short arm (Figure 2b). These findings have been further confirmed by analysis of the phosphorylation of a HORMA domain protein, HIM-3, whose asymmetric enrichment to the SC short arm also depends on the PBD-docking motif

on SYP-1 and the number of crossovers in each nucleus [54].

How the interplay between nucleus-wide and chromosome-autonomous signaling partitions the chromosome relative to the crossover site awaits further study. However, these results are consistent with a speculative model, in which crossover-designated sites nucleate and compete for limiting factors that stabilize the SC in a chromosome-autonomous manner. Sub-threshold levels of crossovers may recruit high levels of such factors, which spill over along the entire chromosome length. This may deplete the soluble pools of SYP proteins below the critical concentration required to maintain the SC on chromosomes without crossovers, leading to their desynapsis [21,23]. A more intense competition is expected as the number of crossovers rises, which will decrease the amount of SC-stabilizing factors recruited to each chromosome. Then, a self-reinforcing mechanism to amplify their effects may yield a faster equilibrium and help establish the short arm relative to the crossover site. The idea of inter-chromosomal competition during crossover formation was initially formulated by Mather in 1936 [55], although it has been largely disfavored due to conflicting evidence. It is possible that this specialized mechanism has been adapted in holocentric nematodes to break the symmetry across the length of holocentric chromosomes and define their segregation pattern in meiosis I.

Concluding remarks

Recent studies have demonstrated how subcellular localization of PLK in meiotic prophase is controlled by elaborate mechanisms that involve not only priming kinases but also other meiotic regulators, a self-reinforcing feedback, and a nucleus-wide crossover-counting mechanism. However, many important questions remain to be addressed. How is the enzymatic activity of PLK-2 regulated during meiotic progression? Although PLK-2-dependent phosphorylation is detected only after the onset of the meiotic program [19,20,56], the mechanism by which PLK-2 is activated remains elusive. Moreover, it is largely unknown how PLK-2 plays such multifaceted functions in orchestrating meiotic chromosome dynamics.

Future identification of PLK substrates will illuminate how this conserved protein kinase family ensures accurate chromosome segregation during meiosis.

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