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SPOTLIGHT

Context is everything: The role of polo-like kinase 1 during *C. elegans* oocyte meiosis

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Meiotic chromosome segregation in oocytes often relies on meiosis-specific modifications of mitotic molecular mechanisms to respond to the unique challenges of this asymmetric division. In this issue, Narula and Wignall (https://doi.org/10.1083/jcb.202503080) demonstrate how the conserved polo-like kinase in *Caenorhabditis elegans*, PLK-1, has been repurposed in unexpected ways to ensure accurate meiotic chromosome segregation during oogenesis.

Meiosis is a specialized cell division program that couples one round of replication to two rounds of chromosome segregation to produce haploid gametes, such as sperm and eggs, for sexual reproduction. Eggs, or oocytes, present a unique challenge to the events of meiotic spindle assembly and accurate chromosome segregation, as demonstrated by the high rates of aneuploidy that accompany oogenesis in humans. At least 35% of all clinically diagnosed miscarriages, as well as infertility, 4% of stillbirths, and numerous types of birth defects, arise predominantly from maternal meiotic errors (1). During oogenesis, spindle assembly occurs in the absence of centrosomes; instead of spindle assembly initiating from centrosomes, spindles are built out from meiotic chromosomes to form an acentrosomal spindle that nonetheless becomes bipolar. Once they have assembled the spindle, oocytes arrest in metaphase of meiosis I or II, depending on the system, and resume meiotic chromosome segregation upon fertilization. Thus, meiotic divisions on an acentrosomal spindle occur even as sperm, that provide both paternal chromosomes and centrosomes for mitotic spindle assembly during embryogenesis, are present. Finally, instead of producing four equal products of meiosis, oogenesis is manifestly asymmetric, generating a large, single gamete and two substantially smaller polar bodies. Thus, the product of oogenesis is a large oocyte that will be developmentally competent to support early embryogenesis after fertilization but whose large volume can compromise accurate chromosome segregation (2). To respond to these challenges and ensure that meiotic spindle assembly and chromosome segregation are coordinated with these and other events, either novel, meiotic factors need to evolve or existing mitotic factors need to be repurposed to take on novel, meiotic roles. In this issue of *Journal of Cell Biology*, Narula and Wignall use acute depletion of PLK-1 to reveal a clear and beautiful illustration of this second scenario (3). They show that PLK-1, an essential polo-like kinase in *Caenorhabditis elegans* that is required for multiple events in mitosis, takes on unexpected meiotic functions to facilitate this coordination.

PLK-1 is a serine/threonine kinase and is one of two polo-like kinases in *C. elegans* but is the only essential one. During mitosis, PLK-1 participates in a complex temporal and spatial orchestration of its activity to accomplish nuclear envelope breakdown, centrosome maturation, spindle assembly, chromosome segregation, and cytokinesis (4). This orchestration is primarily carried out through its polo-box domain. This domain is at the protein's C terminus and binds serines or threonines phosphorylated by other kinases, such as cyclin-dependent kinases, in PLK-1 substrates or proteins associated with PLK-1 substrates (4). Previous work in *C. elegans* demonstrated that PLK-1 plays similar roles in meiotic nuclear envelope breakdown, spindle assembly, and/or maintenance and chromosome segregation (5, 6), suggesting that meiotic roles of PLK-1 mirrored its established, mitotic roles, even when spindles were acentrosomal. Consistent with PLK-1's mode of operation, phosphorylated versions of the chromosomal proteins, BUB-1 and CENP-C, are required for PLK-1's localization to meiotic chromosomes and accurate chromosome segregation (6). How PLK-1 controls meiotic spindle assembly and/or stability was less clear from these studies.

The experiments performed by Narula and Wignall confirm these meiotic roles, particularly the requirement for PLK-1 in both meiotic spindle assembly and stability. However, their acute depletion experiments show additional functions that are in direct contradiction to PLK-1's demonstrated mitotic roles. Specifically, PLK-1 prevents excess microtubule nucleation in other regions of the oocyte and premature centrosome maturation around the sperm-provided centrioles. These excess nucleation events do not appear to recruit proteins that typically organize the spindle poles of acentrosomal spindles, suggesting that their formation relies on other regulators of microtubule nucleation and/or stability, highlighting potential PLK-1 meiotic substrates. Strikingly, PLK-1 localizes to sperm centrioles, presumably to accomplish this inhibition of centrosome maturation, raising the obvious question of how its localization to

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the centrosome during mitosis promotes centrosome maturation, while similar localization to centrioles in meiosis inhibits maturation. Narula and Wignall speculate that their robust depletion experiments reveal these surprising functions, emphasizing the importance of using multiple genetic tools to assess protein function. Altogether, these experiments indicate that PLK-1 function not only promotes key meiotic events but also responds to the challenges of oogenesis to inhibit specific events to ensure that they are appropriately coordinated with meiotic spindle assembly and chromosome segregation. Their work also clearly demonstrates the importance of this coordination, since premature maturation and activation of sperm-derived centrioles in PLK-1–depleted oocytes compromised the positional separation of oocyte and sperm chromosomes, which could have disastrous consequences for completion of oogenesis.

Since Narula and Wignall showed that these phenotypes depend on PLK-1's kinase activity, a clear next topic of research identified by this study is: what are the PLK-1 substrates that explain this meiosis-specific regulation? More specifically, does PLK-1 phosphorylate the same substrates to inhibit centrosome maturation in sperm during oogenesis, or is this different function explained by the phosphorylation of completely different proteins? During mitosis, PLK-1 is recruited to centrosomes by phosphorylated SPD-2 (the *C. elegans* ortholog of human CEP192) to phosphorylate SPD-5 (the functional homolog of CDK5RAP2) and drive centrosome maturation (7, 8, 9). Are these same proteins participating in the inhibition of centrosome maturation on sperm-provided centrioles? Alternatively, PLK-1 may be regulating the microtubule motor kinesin I or its cargo adapter, KCA-1, to limit access of these proteins to centrioles, revealing an altogether separate mechanism (3, 10). Even if PLK-1 is acting through a different regulatory mechanism to inhibit centrosome maturation during meiosis, how are SPD-5 and, presumably, SPD-2 accomplishing centrosome maturation in the absence of PLK-1 activity? Another major question that arises from this work is how is PLK-1 acting spatially to inhibit microtubule nucleation throughout the oocyte, even as it promotes meiotic spindle assembly and stability around meiotic chromosomes? One possible target the authors identify is KLP-7^{MCAK}, a microtubule depolymerase that also produces ectopic microtubule nucleation in both mitosis and oogenesis (3, 11), but other targets may also contribute to this global inhibition.

This rigorous and well-executed study highlights the simple but important reality that we cannot simply assume that regulation of meiotic events is likely to be the same as the regulation of mitotic events, particularly during asymmetric meiotic division in oocytes. Moreover, understanding how meiotic chromosome segregation is regulated and coordinated with events, such as fertilization, to ensure genomic integrity is critical to human reproductive health and early development. Finally, since meiotic proteins are often inappropriately expressed during cancer progression (12), these meiotic-specific mechanisms may explain cancer-specific defects during mitosis, providing an additional link to human health.

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