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Actin together with microtubules in the spindle: Actin prevents chromosome segregation errors during mammalian female meiosis by promoting the formation of functional kinetochore fibers

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Aneuploidy is a condition in which the total number of chromosomes in a cell slightly deviates from the normal diploid number in a given species. It can arise from chromosome segregation problems during meiosis (the process that culminates with the formation of the gametes in the germ line), and is the main cause of age-related female infertility, spontaneous abortions and developmental disorders in humans. Most aneuploidies result in embryonic lethality due to imbalanced gene expression, while others, normally associated with the gain of a single specific chromosome, are compatible with life, such as Down Syndrome (trisomy of chromosome 21 in humans). To segregate chromosomes, cells rely on a rugby ball-shaped microtubule-based structure called the spindle. On page XXX of this issue, Mogessie and Schuh (1) show that another cytoskeleton filament - actin - can be found in close association with microtubules in the spindle and promotes chromosome segregation fidelity during meiosis I and II in mammalian oocytes.

The role of actin in chromosome segregation has been a long-standing debate in the field. While there is compelling evidence that microtubules are critical elements for chromosome segregation, Forer, Pickett-Heaps and others have defended for decades that, at least for some cell types, poleward chromosome movement during anaphase might be assisted by non-microtubule elements in the spindle, such as actin and myosin (2). Actin and myosin forms have been identified in the spindle of a wide range of cell types and species, including humans (3, 4). Experimental disruption of actin filaments with high concentration of cytochalasins in insect spermatocytes affected poleward chromosome movement and caused lagging chromosomes during meiosis I (5, 6). However, these findings were difficult to reproduce in other systems, notably in many mammalian somatic cells undergoing mitosis [discussed in (7)].

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Based on beautiful fixed- and live-cell imaging, Mogessie and Schuh now report with unprecedented resolution the presence of an “actin spindle” in oocytes from several mammalian species, including humans (1). Pharmacological or genetic perturbation of actin dynamics during meiosis I and II resulted in lagging chromosomes that moved poleward at reduced velocities during anaphase. Similar actin perturbations also prevented chromosome congression and maintenance of alignment at the spindle equator, but only in meiosis II. Curiously, the “actin spindle” only became detectable late in meiosis I, which might explain why actin was only required for chromosome congression during meiosis II. Actin depolymerization caused a reduction in the microtubule density on kinetochore fibers that attach to chromosomes, whereas microtubule depolymerization led to the disassembly of the “actin spindle”. Expression of an engineered microtubule-actin crosslinker promoted the bundling of kinetochore fibers. Overall, they proposed that actin accounts for accurate chromosome congression and segregation in mammalian oocytes by promoting the formation of functional kinetochore fibers.

But how does actin promote kinetochore fiber formation? The authors showed that the mechanism is independent of actin’s role in vesicle transport and cytokinesis. It is also distinct from the previously proposed role of an actin mesh in chromosome congression in starfish oocytes, as a way to collect chromosomes dispersed over tens of micrometers from the spindle region (8). The idea of an “actin spindle” that assists microtubule bundling at kinetochores is appealing, but difficult to test experimentally. Consistent with the observations now reported in mammalian oocytes, correlative light and electron microscopy studies after actin disruption in vertebrate cells in culture revealed remarkably similar perturbations in mitotic spindle microtubule organization and kinetochore structure, including reduction and fragmentation of kinetochore microtubules, leading to chromosome congression and segregation defects (9, 10). However, global perturbation of actin in mammalian oocytes would also disrupt the well-known actin mesh that fills the cytoplasm around the microtubular spindle and plays a role in spindle positioning (4). The development of new tools that would allow the dissection of actin function in time and space (e.g. with optogenetics) will be essential to understand how an “actin spindle” would prevent chromosome segregation errors during meiosis, while investigating how this might change with ageing. Finally, it remains unclear whether the proposed role of actin in kinetochore fiber formation relies on a contractile mechanism dependent on myosin, and what is the nature of the actin-microtubule crosslinking molecules. On this front, CLASPs appear as excellent candidates, as they are known to bundle spindle microtubules (11), they bind both to microtubules and actin (12) and their overexpression rescued the kinetochore fiber phenotypes observed after actin perturbation in mammalian oocytes (1).

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Figure. How actin promotes chromosome segregation during female meiosis.

Actin was known to be required to relocate the spindle to the cortex and for extrusion of the polar bodies during cytokinesis. Mogessie and Schuh now report that actin assembles into a microtubule-dependent spindle-like structure and promotes kinetochore fiber (k-fiber) formation during meiosis. Actin disruption causes chromosome congression problems during meiosis II and compromises chromosome segregation fidelity in both meiosis I and II.