An actin shell delays oocyte chromosome capture by microtubules

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The large nuclei and tiny spindles of oocytes create a challenge for chromosome capture at M-phase entry. A contractile F-actin mesh in starfish oocytes delivers chromosomes to the spindle and Burdyniuk et al. (2018. J. Cell Biol. https://doi.org/10.1083/jcb.201802080) show that F-actin delays the capture of chromosomes until they are within reach of microtubules.

The oocyte nucleus is extremely large across species as its size scales with the dimension of the cell, as is the case for many organelles. The starfish oocytes nucleus is 70 µm wide and thus when meiosis resumes and the nuclear envelope breaks down, most chromosomes are out of reach of spindle microtubules. This is a result of dynamic instability of microtubules in M-phase, which limits their size to a maximum of 30–40 µm long in this model system and therefore limits their capacity to capture chromosomes dispersed in a volume of larger dimensions (Mitchison and Kirschner, 1984). This limit is particularly critical for chromosomes that are further away from the animal pole. Prior work from the Lénárt laboratory has shown that a contractile actin fishnet efficiently gathers all chromosomes and delivers them to the animal pole of the oocyte, where the two centrosomes reside (Mori et al., 2011; Borrego-Pinto et al., 2016). The first meiotic spindle further assembles from these two centrosomes and anaphase I proceeds thereafter. In this issue, Burdyniuk et al. examine the specific transition between chromosome delivery by actin and the capture of kinetochores by spindle microtubules. In particular, they address how the capture by microtubules is coordinated to the delivery of bivalents at the animal pole, as the rapid spindle assembly, around 30 min in this species, makes coordination essential. If either the delivery by the actin network or the coordination between delivery and capture do not occur, chromosomes will be lost in the huge cytoplasmic volume resulting in the formation of an aneuploid starfish oocyte. Here, Burdyniuk et al. (2018) discover a novel mechanism by which oocytes can compensate for the major disadvantage of having to congress their chromosomes inside a huge volume, an issue very important and specific to meiosis I. Interestingly it is long established that human female meiosis I is more error prone than meiosis II (Hassold and Hunt, 2001). Also, during female meiotic divisions in all species studied so far, there is no reformation of a meiotic spindle further assembles from these two centrosomes and anaphase I proceeds thereafter. In this issue, Burdyniuk et al. (2018) analyze in great depth the motion of chromosomes around the time of nuclear envelope breakdown (NEBD) in starfish oocytes. The movement of chromosomes can be described as biphasic. In a first phase lasting ~8 min, it is slow (~0.5 µm/min) and not directional; it then becomes faster (~9 µm/min) and directed toward the two centrosomes anchored at the cortical animal pole (Fig. 1). These velocities are compatible with respective forces exerted on chromosomes by F-actin and microtubules in other oocyte models (Verlhac et al., 2000; Tanimoto et al., 2016). The addition of an actin-depolymerizing drug right after NEBD confirms that the first phase is actin dependent. The second phase, however, depends on microtubules and dynein activity. Importantly, Burdyniuk et al. (2018) noticed that inducing actin depolymerization had an unexpected effect: chromosomes were captured earlier than when actin was present. This suggests that actin has an inhibitory effect on the capture of kinetochores by microtubules. This effect is not a result of the presence of a contractile actin mesh since authors could show, first, that densification of this mesh does not prevent chromosome capture and, second, that forces exerted by microtubules can tear the actin mesh apart.

The authors then focused their attention toward another actin structure present at that stage, namely, patches of F-actin around chromosomes (Lénárt et al., 2005). They show that one subunit of the Arp2/3 F-actin nucleator complex, ArpC1, is enriched on chromosomes a few minutes after NEBD. Interestingly, ArpC1 accumulates on distal chromosomes, close to the nuclear envelope more
than on chromosomes inside the nucleus (Fig. 1, in phase I, stronger patches are represented for chromosomes in the periphery of the nucleus). This accumulation of ArpC1 correlates with the accumulation of F-actin patches. They are both transient, disappearing concomitantly with the end of phase I, after 8 min. Consistent with the nucleation by the Arp2/3 complex, these patches disappear after treatment of oocytes with CK666, an Arp2/3 inhibitor, added after NEBD. Chromosomes are active players in their capture, organizing their own actin shell in a dynamic manner. Indeed, altering RanGTP levels, using either dominant-negative or constitutively active Ran mutants, prevents the local accumulation of ArpC1 and F-actin around chromosomes. This observation is reminiscent of previous work from mouse oocytes where the RanGTPase activated around chromosomes promotes local Arp2/3-dependent nucleation of cortical actin patches (Deng et al., 2007). It is noteworthy that in both models the intensity of patches is stronger when chromosomes are apposed to a nuclear or plasma membrane. This might suggest a positive feedback loop provided by membranes for Arp2/3-mediated nucleation.

Specific tools to depolymerize either the actin contractile mesh or the actin patches are unfortunately not yet available. Hence it is still difficult to precisely distinguish their relative contribution in the actin-driven motion of chromosomes toward the animal pole or in delaying the capture of chromosomes by microtubules. Nevertheless, Burdyniuk et al. (2018) provide convincing evidence that depolymerization of actin patches correlates more with chromosome capture by microtubules than depolymerization of the actin net in physiological conditions as well as after treatment with an actin-depolymerizing drug.

To determine the role of these actin patches, the authors turned to modeling using the Cytosim software. This modeling allowed them to demonstrate that the search and capture model (Mitchison and Kirschner, 1984) is not sufficient to collect all chromosomes in the huge volume of the nucleus when meiosis resumes. Adding to the search and capture model, the gathering effect provided by the contractile fishnet allows for the capture of all chromosomes. Yet, the simulation shows that capture would start right at NEBD, which experimentally is not the case (it is delayed until 8 min after NEBD). To reproduce the experimental observations, it is necessary to add to the simulation a transient block ingredient that delays chromosome capture. Then the simulation recapitulates the physiological process of progressive coordination of chromosome capture. F-Actin patches would transiently block access to microtubule by steric hindrance, providing a delay until all chromosomes are in the vicinity of the centrosomes to initiate efficient biorientation.

Modeling is used in a very elegant manner here. First, it circumvents the technical issue of addressing how F-actin patches can affect capture by microtubules. Second, it proposes a novel working hypothesis of antagonistic roles between F-actin and microtubules in their interactions with kinetochores. Many interesting questions remain to be addressed in the future. For example, what triggers the initial assembly of F-actin patches around chromosomes at NEBD? Is it due to local activation of a nucleation-promoting factor via phosphorylation by M-phase kinases? Why are patches stronger for chromosomes further away from the centrosomes? Is this somehow correlated with the progression of the wave of NEBD observed in this model system? Similarly, how are these patches disassembled and what signal triggers this? Is this also coordinated with progression into the cell cycle? The actin patches not only delay kinetochore capture but they may also protect bivalents from early interactions with kinetochore fibers. One could imagine that early interactions could promote breakage of chromosomes. It remains puzzling that in many species these interactions appear to be delayed during oocyte meiosis I (Bennabi et al., 2016).
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