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An actin fishnet for DNA

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Abstract

It has long been thought that gathering chromosomes during spindle assembly is exclusively the responsibility of microtubules. However, a recent study by Lénárt *et al.* shows that, in larger cells, a collapsing network of actin filaments ensnares and transports the chromosomes, bringing them in range for microtubule capture.

Spindle assembly in the oocyte is arguably one of the most important and impressive cellular events during the lifetime of an animal. Its importance stems from the fact that failed or improper transmission of genetic information so early in development has drastic consequences, including sterility and birth defects. Its impressiveness is due to the relatively enormous size of both the oocyte and its nucleus (germinal vesicle), and from the fact that the spindle is asymmetrically anchored at one end of the cell. Because germinal vesicles typically range in size from 20 to more than 300 μm , the assembly of the first meiotic spindle in oocytes entails movement of the chromosomes over distances of 30–400 μm or more¹ (Fig. 1a).

How is this accomplished? Work in mitotic cells and cell extracts indicates that chromosome congression is the exclusive province of microtubules, which extend from the separating microtubule-organizing centres and capture (or are captured by) the condensing chromosomes². This ‘search-and-capture’ mechanism, in combination with spindle self-assembly through microtubule-motor-dependent pushing and pulling, is thought to position the chromosomes at the metaphase plate². However, using a combination of live cell imaging and specific pharmacological manipulations, Lénárt *et al.*³ now show that in starfish oocytes, the microtubules are simply not long enough to reach the far-flung chromosomes. Instead, the initial phases of chromosome congression result from a ‘fishnet’ of F-actin that assembles rapidly upon germinal vesicle breakdown, surrounds the chromosomes and then collapses inwards, thereby trawling the chromosomes to the site of the nascent spindle, where they are captured by microtubules (Fig. 1b). The relative importance of this actin network in chromosome congression is perhaps best illustrated by the fact that without F-actin, many of the chromosomes remain scattered in the cytoplasm, whereas without microtubules all of the chromosomes cluster at approximately the right location, in spite of the complete absence of a spindle.

These findings not only reveal a new and critically important role for F-actin, they also represent a striking role reversal for the actin and microtubule cytoskeletons. That is, it is generally thought that microtubules and microtubule motors represent the long-range transport system for vesicles and other cargo in cells, whereas actin filaments and myosin motors are believed to take care of short-range transport at the cortex⁴. Here, in contrast, it is the actin cytoskeleton that is responsible for long-range transport, whereas microtubules direct the local traffic.

In addition to shaking up our basic view of spindle assembly and cytoskeletal function, this study prompts a series of fascinating and important questions: first, to what degree is the actin fishnet mechanism conserved? With respect to oocytes in other species, there is ample evidence that the actin cytoskeleton is required for one or more steps in assembly or positioning of the first meiotic spindle^{5,6}, and it will be important to now apply the approaches used by Lénárt *et al.* to determine whether or not a network of F-actin is required for chromosome congression *per se*. However, the potential role for this actin network is not restricted to oocytes. The nucleus is a repository for actin regulatory proteins not only in oocytes⁷, but also in mitotic cells^{7,8}. And whereas microtubules may be sufficient for chromosome congression in smaller cells, the potential for actin abetting this process has not, to our knowledge, been directly tested.

Second, what is the nature of the signal(s) that triggers the actin network to assemble? In the new study the chromosomes themselves, as well as DNA-coated beads, serve as sites of local actin accumulation, an event that presumably ensures their incorporation into the actin network. However, the network extends well beyond the chromosomes, and ensnares the entire disassembling germinal vesicle. Because assembly of the network is temporally correlated with disassembly of the germinal vesicle envelope, it is likely that one of the key signals is provided when the cytoplasm and the nucleoplasm mix. On the other hand, Lénárt *et al.* note that tearing a hole in the germinal vesicle before the onset of meiotic maturation does not result in local actin assembly. Thus, progression through the cell cycle must also be required. The authors also find that although there is actin in the germinal vesicle prior to induction of meiotic maturation⁹, it is apparently unable to assemble into filaments, because phalloidin injection does not result in formation of nuclear F-actin at this stage. So, the results presented by Lénárt *et al.* argue that a combination of cell-cycle progression and nucleoplasm–cytoplasm mixing allows the inhibition of nuclear actin assembly to be rapidly relieved.

Third, how does the actin fishnet accomplish its task of bringing chromosomes into range for efficient capture by microtubules? At least two distinct but overlapping features of this process must be considered: first, the mechanism that powers fishnet collapse; and second, the mechanism that directs the exchange from actin-mediated to microtubule-mediated chromosome transport. One possibility is that collapse could result from motor activity. Although the polarity of actin filaments in the fishnet is not known, motor-driven collapse could, in principle, happen even if the F-actin network does not have overall polarity. Precedence for this is seen in actin networks made of purified F-actin and myosin motors, which undergo progressive contraction in the presumptive absence of any initial F-actin polarity¹⁰. The only theoretical requirement is that the myosins in question have at least two

actin-binding sites, organized in a way that permits antiparallel contraction, as would be the case for myosin-2 and certain myosin-1s¹⁰. In other words, as seems to be the case for the spindle², self-assembly may have an important role in actin fishnet function. Alternatively, fishnet collapse could be due to differential actin disassembly, as suggested by Lénárt *et al.* Consistent with this mechanism, they see that actin fishnet collapse and chromosome congression are sensitive to inhibition of F-actin turnover, and previous *in vitro*¹¹ and *in vivo*¹² studies indicate that directed movement can be powered by actin network disassembly. It is also feasible that myosin motors work together with differential disassembly to drive fishnet collapse. Indeed, Lénárt *et al.* observe streaming of F-actin cables towards the animal pole but no apparent increase in network brightness, suggesting that both myosin activity and actin disassembly might be concentrated in that region. Given the recent demonstrations that myosin-2 is required for F-actin disassembly in the cytokinetic apparatus^{13,14}, and that myosins associate with the first meiotic spindle^{15,16}, it is even conceivable that the same motor is responsible for both movement and disassembly of the fishnet.

Once collapse has ensued, how is the transition from actin- to microtubule-mediated transport accomplished? Lénárt *et al.* show that the chromosomes exhibit two distinct phases of movement: first, a slow phase in which chromosomes move in an actin-dependent manner at $\sim 3 \mu\text{m min}^{-1}$, and then a fast phase in which chromosomes move at $>12 \mu\text{m min}^{-1}$ in a microtubule-dependent manner. But it is unclear how the chromosomes are handed off from the actin-mediated to the microtubule-mediated regime.

One possibility is that the actin network simply constricts, and once the chromosomes are within range, microtubule search-and-capture can take effect. Interestingly, however, there does not seem to be any lag time between the two phases of chromosome movement, suggesting that the handoff is highly efficient. Alternatively, the microtubules may be led to the actin-engulfed chromosomes in a more directed manner; it is conceivable that the actin network could help target the microtubules to chromosomes by providing actin filament tracks that microtubules bind to and grow along¹⁷. Such coordination would probably use one of the growing number of proteins known to crosslink F-actin and microtubules¹⁷. If microtubules are in fact directed to chromosomes on a highway of actin filaments to make search-and-capture more efficient, this could provide a rationale for this mechanism to be implemented in a wider range of cellular contexts. Indeed, mathematical modelling studies show that search-and-capture is not efficient enough to explain the experimentally observed duration of spindle assembly unless some factor biases the microtubules towards the chromosomes¹⁸. While cues from the chromosomes that promote microtubule assembly might provide one such bias¹⁹, an actin network might be another.

Answering the above questions should be a high priority for specialists in the field. And even for those only casually interested in cell division and the cytoskeleton, the paper by Lénárt *et al.* as well as other recent work^{6,16,20} strongly suggests that both meiotic and mitotic spindle assembly may be far more dependent on the actomyosin cytoskeleton than has generally been appreciated.

References

1. Lénárt P, Ellenberg J. *Curr Opin Cell Biol.* 2003; 15:88–95. [PubMed: 12517709]
2. Gadde S, Heald R. *Curr Biol.* 2004; 14:R797–R805. [PubMed: 15380094]
3. Lénárt P, et al. *Nature.* (in the press). 10.1038/nature03810
4. Rogers SL, Gelfand VI. *Curr Biol.* 1998; 8:161–164. [PubMed: 9443916]
5. Gard DL, Cha BJ, Roeder AD. *Zygote.* 1993; 3:17–26. [PubMed: 7613871]
6. Leader B, et al. *Nature Cell Biol.* 2002; 4:921–928. [PubMed: 12447394]
7. Ankenbauer T, et al. *Nature.* 1989; 342:822–825. [PubMed: 2689884]
8. Holaska JM, Kowalski AK, Wilson KL. *PLoS Biol.* 2004; 2:1354–1362.
9. Clark TG, Rosenbaum JL. *Cell.* 1979; 18:1101–1108. [PubMed: 574804]
10. Fujisaki H, Albanesi JP, Korn ED. *J Biol Chem.* 1985; 260:11183–11189. [PubMed: 4030787]
11. Hellewell SB, Taylor DL. *J Cell Biol.* 1979; 83:633–648. [PubMed: 42649]
12. von Dassow G, Schubiger G. *J Cell Biol.* 1994; 127:1637–1653. [PubMed: 7798318]
13. Murthy K, Wadsworth P. *Curr Biol.* 2005; 15:724–731. [PubMed: 15854904]
14. Guha M, Zhou M, Wang YL. *Curr Biol.* 2005; 15:732–736. [PubMed: 15854905]
15. Simerly C, Nowak G, de Lanerolle P, Schatten G. *Mol Biol Cell.* 1998; 9:2509–2525. [PubMed: 9725909]
16. Weber KL, et al. *Nature.* 2004; 431:325–329. [PubMed: 15372037]
17. Rodriguez OC, et al. *Nature Cell Biol.* 2003; 5:599–609. [PubMed: 12833063]
18. Wollman R, et al. *Curr Biol.* 2005; 15:828–832. [PubMed: 15886100]
19. Carazo-Salas RE, Karsenti E. *Curr Biol.* 2003; 13:1728–1733. [PubMed: 14521840]
20. Rosenblatt J, Cramer LP, Baum B, McGee KM. *Cell.* 2004; 117:361–372. [PubMed: 15109496]

Figure 1.

Schematic diagram illustrating congression in oocytes. **(a)** Upper part: during cell-cycle progression, an oocyte (left) must somehow congress its chromosomes (blue) over large distances such that in the egg (right) the DNA is attached by microtubules (red) to the animal pole in the first meiotic spindle. Lower part: approximate and relative distances that chromosomes must travel during congression in mitotic cells and different oocytes. **(b)** The actin fishnet (green) surrounds the chromosomes (blue) and collapses inwards, bringing the chromosomes in range of the microtubules (red), which ultimately position the chromosomes at the plasma membrane in the meiotic spindle.