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Chromosome Congression: Another Fine Mesh We've Gotten into

Collecting chromosomes prior to their accurate distribution by the mitotic spindle is widely believed to be a microtubule-driven process. However, a recent study in *Nature* by Lénárt et al. (2005) has revealed that a contractile actin network makes an essential contribution to chromosome capture in animal oocytes.

Cells vary widely in size and architecture, yet in order to divide successfully, each must assemble a bipolar spindle to accurately segregate its genome. In a "typical" animal cell, this process begins when the nuclear envelope breaks down and condensed chromosomes are exposed to microtubule polymers emanating from two nucleating sites (centrosomes). Dynamic cycles of microtubule growth and shrinkage facilitate "search and capture" of the chromosomes, which together with the activities of many factors including microtubule-based motor proteins, generates a bipolar structure in which sister chromosomes are attached to spindle microtubules and facing opposite spindle poles, where they are transported during anaphase (Gadde and Heald, 2004).

However, life is not so simple in many cell types. A striking example is the animal oocyte, in which the nuclear (germinal vesicle) diameter can range up to hundreds of microns, 1–2 orders of magnitude greater than that of a fibroblast (Lénárt and Ellenberg, 2003). This creates a problem for spindle assembly. Rapid microtubule turnover promotes "search and capture" of the chromosomes, but it also limits the steady-state length of microtubules, potentially putting oocyte chromosomes out of their reach. Even if there were a bias of microtubule growth toward chromosomes, computer simulations predict that the efficiency of microtubule capture would decline rapidly at chromosome-centrosome distances greater than 30 microns (Wollman et al., 2005). Lénárt et al. (2005) investigated this issue by high-resolution imaging of starfish oocytes undergoing meiosis I, and indeed observed that chromosomes were often not within range of the microtubules. Nevertheless, chromosomes were gathered into the spindle at the cell cortex of the animal pole, but how? Providing the first evidence for a nonmicrotubule element of chromosome capture, Lénárt et al. (2005) go on to show that an actin network functions to gather the chromosomes to the area of the forming spindle. The relative importance of actin and microtubules in chromosome congression is well illustrated by comparing the effects of their pharmacological inhibition. Without actin polymerization, many of the chromosomes remain scattered throughout the cytoplasm, whereas without microtubules, all of the chromosomes collect at approximately the right location, even though a spindle does not form.

How does actin drive chromosome movement? Precisely at germinal vesicle breakdown, Lénárt et al. (2005) observed massive actin polymerization at the inner nuclear rim, which then depolymerized except for dense patches around chromosomes that persisted as the actin mesh contracted, delivering the chromosomes to the animal pole at a rate of ~3 μm/min. Patch disappearance correlated with a phase of rapid movement (>12 μm/min) due to microtubule-dependent capture (Figure 1).

These exciting results reveal a new and important cellular role for actin and raise a stimulating series of questions. What triggers the formation and collapse of the actin network, and how does this process collect the chromosomes precisely where the meiotic spindle is to form? When exposed to the cytoplasm at envelope breakdown, nuclear actin is stimulated to polymerize at the periphery by some cell cycle-dependent mechanism, as the authors note that premature tearing of the membrane did not cause actin assembly. To contract the network, two possible mechanisms seem likely and are not mutually exclusive. Motor activity, in the form of crosslinking myosins, could promote actin filament

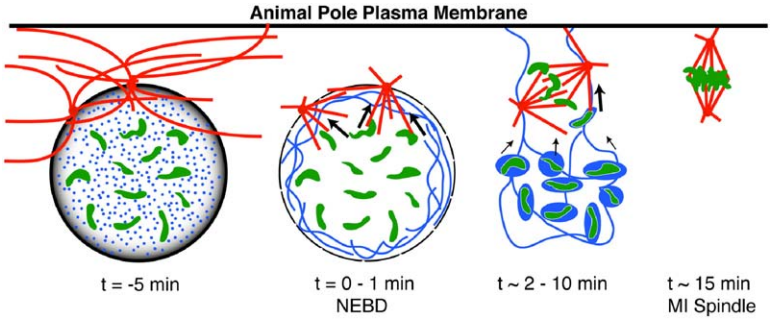

Figure 1. Schematic of Meiosis I Progression in a Starfish Oocyte

Prior to nuclear envelope breakdown (NEBD), a large microtubule array (red) is present at the animal pole cortex, while unpolymerized actin (blue) and chromosomes (green) reside in the nucleoplasm of the large germinal vesicle. At NEBD, short microtubule asters grow from centrosomes while an actin filament shell polymerizes at the periphery of the fragmenting nucleus. Chromosomes located near the centrosomes are rapidly captured by microtubules (large bold arrows). The peripheral actin network is cleared within several minutes, leaving actin patches around the lagging chromosomes, which are connected by a network of actin filaments and slowly transported (small arrows) toward the spindle, where rapid microtubule capture occurs. Thus, within about 15 min of NEBD, the concerted action of actin and microtubules leads to proper congression of chromosomes onto the metaphase plate of the MI spindle.

bundling and contraction, a phenomenon that has been visualized in *Xenopus* egg extracts (Waterman-Storer et al., 2000). Alternatively, localized depolymerization of the actin network could bring about its collapse. In support of this idea, Lénárt and colleagues observed that treatment of the starfish eggs with actin-stabilizing drugs after germinal vesicle breakdown inhibited chromosome movement and network contraction. Regardless of the contraction mechanism, it must somehow be linked to the animal cortex, through physical attachment of the network and/or specific localization of regulatory factors. The centrosomes, which are positioned at this site, provide a potential cue. By virtue of their associated actin patch, individual chromosomes ensnared in the mesh could then be reeled in.

Interestingly, the actin patch-forming activity of chromosomes could be mimicked by injecting DNA-coated beads into oocytes, raising the possibility of dissecting aspects of this pathway in vitro with egg extracts. Such an approach would allow individual components to be specifically depleted and their contribution evaluated. However, the association of actin networks with chromosomes was transient, fading just when the chromosomes came into microtubule range. These observations have two remarkable implications: that in addition to having biochemical activity toward microtubules (Gadde and Heald, 2004), chromatin can also influence actin; and that there is interaction between the two cytoskeletal elements and their dynamics at chromosomes. Conserved mechanisms are known to link actin and microtubules during other cellular morphogenetic events (Rodriguez et al., 2003), and it will be of great interest to elucidate their connection at chromosomes.

In addition to understanding its mechanisms, a second major issue stemming from this work is the degree of conservation of this actin network pathway in chromosome capture. There is already evidence that the actin cytoskeleton is important for meiosis in other oocytes, though the interpretation has focused more on a role for cortical actin in spindle anchoring and positioning (Gard et al., 1995, Weber et al., 2004, Leader et al., 2002). It will be informative to apply the approaches of Lénárt and colleagues to examine chromosome movements in these systems. And what about in a "typical" animal cell? Microtubule-dependent capture appears to be sufficient in small cells, but interaction of the spindle with the cortical actin cytoskeleton facilitates spindle assembly under some circumstances (Rosenblatt et al., 2004). If there is a lesson about mitosis, it is that redundancy is rampant. Although it may be obvious only in large cells, an actin-mediated mechanism may serve to bolster chromosome capture in small cells as well. Interplay among cytoskeletal elements once believed to have distinct functions is the emerging theme.

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