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Previews

Symmetry Breaking in *C. elegans*: Another Gift from the Sperm

Polarization of the *C. elegans* embryo depends on the sperm-contributed centrosome, which cues a retraction of the actomyosin cortex to the opposite end of the embryo by an unknown mechanism. New evidence reveals that the sperm donates a second polarizing cue that may locally relax the actomyosin cortex near the point of sperm entry.

One of the first jobs most animals tackle is breaking symmetry, as initially symmetrical eggs become embryos that will need to develop a distinct front end and back end. *C. elegans* has been a popular model for investigating symmetry breaking using a diverse array of experimental tools, including tools of genetics, molecular biology, live microscopic imaging, and computational modeling. New work is beginning to fill long-standing gaps in the explanation of how symmetry is broken in the *C. elegans* embryo.

Early work on *C. elegans* embryos used genetic methods to identify many of the critical regulators of symmetry breaking, most notably, the PAR proteins, which have since been found to be highly conserved regulators of cell polarity (see Schneider and Bowerman, 2003, for review). Certain PARs, including PAR-2, localize to the posterior end of the one-cell stage embryo, while other PARs, including PAR-3 and PAR-6, localize to the anterior end. Both the anterior and the posterior PAR proteins are essential for localization of cell fate determinants and spindle positioning before the first cell division. When the PAR proteins' functions are disrupted, the embryo remains symmetrical and fails to develop normally.

What acts upstream to localize the PAR proteins to distinct domains? Manipulating the location of sperm entry showed that the sperm carries the cue that polarizes the embryo. Further experiments demonstrated that while the sperm nucleus is dispensable for polarization, maturation of the sperm-derived centrosome is essential for polarization, suggesting a centrosome or microtubule driven mechanism (see Schneider and Bowerman, 2003, for review). Conflicting results have left uncertain whether microtubules play an essential role in polarization (Wallenfang and Seydoux, 2000; Cowan and Hyman, 2004; Sonneville and Gönczy, 2004).

Several recent advances have shed light on how a sperm-derived cue may polarize the embryo (Cheeks et al., 2004; Munro et al., 2004). A network of actin and myosin II forms at the cortex of the egg. After fertilization and completion of meiosis, this network undergoes a myosin-dependent retraction toward the anterior of the embryo, coalescing in foci of actin and myosin on the anterior side of the embryo. As it retracts, this cortical network takes with it the anterior PAR proteins such as PAR-3 and PAR-6, allowing PAR-2 to become cortically localized at the other end of the embryo, thereby setting up the initial polarized distribution of the PAR proteins (Figure 1). The myosin-driven cortical movements also result in opposing central movements that carry cytoplasmic determinants toward the site of sperm entry.

Three papers now show that these actomyosin contractions are regulated by the small GTPase Rho, which activates myosin, most likely through a Rho-associated kinase (Jenkins et al., 2006; Motegi and Sugimoto, 2006; Schonegg and Hyman, 2006). In embryos lacking RHO-1, myosin activation fails to occur, the actomyosin network fails to form normally, and anterior PAR proteins remain uniformly distributed along the anteroposterior axis of the embryo. Rho family GTPases are commonly regulated by two classes of proteins: RhoGEFs, which activate Rho signaling by triggering GDP/GTP exchange, and RhoGAPs, which inactivate Rho signaling by catalyzing GTP hydrolysis. The *C. elegans* RhoGEF ECT-2 likely activates RHO-1, since removal of ECT-2 phenocopies RHO-1 removal, resulting in failure of myosin activation, cortical contraction, and PAR-6 localization.

The Mango lab has studied the *C. elegans* RhoGAP CYK-4 for its role in epithelial cell polarization in the *C. elegans* foregut, and they report now that CYK-4 protein is also associated with membranous organelles of the sperm (Jenkins et al., 2006). Sperm-derived CYK-4 is deposited in the egg at fertilization, and it remains for some time in a bolus at the point of sperm entry. RNAi experiments show that CYK-4 is important for polarizing the one-cell embryo, and, by generating embryos in which the CYK-4 is contributed only by the egg or only by the sperm, Jenkins and colleagues can demonstrate that polarization depends critically on the sperm-contributed CYK-4. The results suggest that the sperm-contributed bolus of CYK-4 may act as a localized cue for polarization (Figure 1). CYK-4's RhoGAP domain may allow it to locally relax the actin cytoskeleton by acting antagonistically to the Rho signaling that activates contractility in the rest of the cell cortex. In support of this, Jenkins et al. show that the actomyosin network in *cyk-4(RNAi)* embryos fails to retract to one side of the embryo even though it coalesces into large foci, suggesting that the network is contractile but not polarized in the absence of CYK-4.

The new results, together with previous work, suggest a model in which a contractile actomyosin network is stretched around the cortex of the embryo, and sperm-donated CYK-4 locally disassembles the network by locally downregulating Rho-mediated myosin activation, leaving a gap in the network near the site of sperm entry. Contraction of the punctured network to the opposite end of the embryo draws with it the anterior PARs, allowing the posterior PARs to bind to the posterior cortex, and also driving central cytoplasmic determinants to the posterior in an opposing flow. CYK-4 is a key player in this model, generating the initial gap that sets the cortex in motion.

What, then, does the sperm centrosome do? Centrosome-nucleated microtubules have been implicated in locally disassembling an actin network in a number of

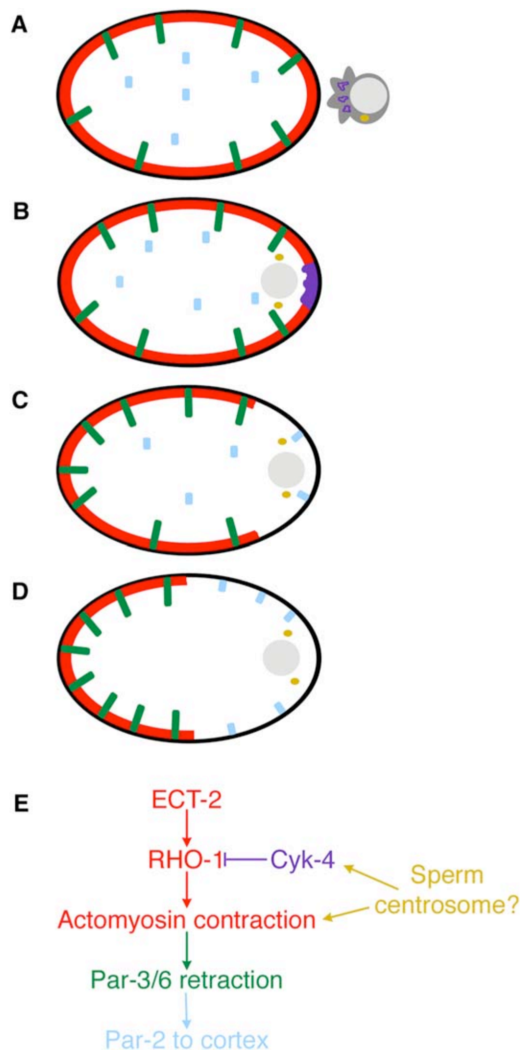

Figure 1. Polarization of *C. elegans* by Sperm-Contributed Cues

Fertilization (A) imparts two sperm-derived components that are essential for polarization (B), CYK-4 (purple) and the pair of centrosomes (orange) derived from the single sperm centrosome. The sperm nucleus (gray) is dispensable for polarization. Polarization signals lead to contraction of the actomyosin network (red), which carries the anterior PAR proteins (green) (C). This allows access to the cortex for the posterior PAR complex (blue) (D). (E) diagrams the regulatory pathway involved in this process.

systems, although exactly how this works has never been completely clear. In *C. elegans* embryo polarization, the centrosome or associated microtubules might act in parallel with CYK-4, or they might act as an integral part of a CYK-4 mechanism. For example, CYK-4 is known to be recruited to microtubules during cytokinesis by the kinesin-like protein ZEN-4 (Mishima et al., 2002). While ZEN-4 is not required in polarization, it is possible that alternative or redundant partners may link CYK-4 to microtubules after fertilization. This might enable centrosomes to temporally regulate polarization of the embryo, waiting to drive polarization until meiosis completes by delaying delivery of CYK-4 to the cell cortex until centrosome maturation.

With two symmetry-breaking cues contributed by the sperm in *C. elegans*, which one acts as a positional cue, or do both share this job? Does one act as a positional cue and the other as a temporal cue? Rho activity and centrosomes have both been recognized as important players in cell polarization in a variety of systems. The new results suggest that changing the position or timing at which both centrosomes and CYK-4 function in *C. elegans* may help determine how these cues function in cell polarization.

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Smad7: Licensed to Kill β-Catenin

Elevated levels of inhibitory Smad7 are detected in several pathologic skin conditions; however the functional consequences of this expression have been unclear. A recent study shows that Smad7 overexpression in transgenic mouse epidermis at levels comparable to those seen in pathologic states is insufficient to block TGFβ or BMP signaling, but instead produces striking phenotypes due to degradation of β-catenin through a novel mechanism involving Smad7 and Smurf2.