Leading Edge
Review

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Cell Polarity in Eggs and Epithelia: Parallels and Diversity

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Cell polarity, the generation of cellular asymmetries, is necessary for diverse processes in animal cells, such as cell migration, asymmetric cell division, epithelial barrier function, and morphogenesis. Common mechanisms generate and transduce cell polarity in different cells, but cell type-specific processes are equally important. In this review, we highlight the similarities and differences between the polarity mechanisms in eggs and epithelia. We also highlight the prospects for future studies on how cortical polarity interfaces with other cellular processes, such as morphogenesis, exocytosis, and lipid signaling, and how defects in polarity contribute to tumor formation.

Introduction

Most animal cells display obvious polarity, indicating the presence of molecular asymmetries. The general steps of cell polarity, including its establishment and transduction, are common irrespective of cell type or organism: a polarity cue, regulation of the cytoskeleton, dedicated polarity proteins, and transduction of polarity information. The initial steps of polarity have mechanistic parallels in different cell types, and PAR proteins exemplify this conservation. Identified through seminal work from Ken Kemphues and colleagues in the *C. elegans* zygote (Kemphues et al., 1988; Suzuki and Ohno, 2006), PAR proteins are conserved and dedicated regulators of polarity in animal cells. Of particular importance are PAR-3, PAR-6, and aPKC (atypical protein kinase C), which form an asymmetrically localized complex in many polarized cells (Suzuki and Ohno, 2006). Although initial work in different organisms suggested a simple view of obligate interactions between PAR proteins, it is now clear that equally important roles are played by complexes containing both PAR and non-PAR proteins and by independent polarity complexes. To illustrate the congruence and diversity of cell polarity mechanisms, we focus on cell polarity in two different cell types: eggs and epithelia.

Establishing Polarity in the *C. elegans* Embryo

The one-celled embryo of *C. elegans* is one of the best understood and most experimentally amenable systems for studying the induction and transduction of polarity. Over the course of 1 hr after fertilization, the oocyte transforms into a highly polarized one-cell embryo that divides asymmetrically to give rise to cells of different sizes, contents, cell-cycle times, and developmental potentials (Figure 1). Where and when does polarity arise? The key event is the negative regulation of actomyosin contractility, which is triggered locally by a sperm cue.

The *C. elegans* oocyte, arrested in prophase of meiosis I, has no developmentally significant polarity (Goldstein and Hird, 1996). After fertilization and the completion of meiosis, the oocyte nucleus (i.e., the pronucleus) and the sperm pronucleus/centrosome complex are usually found at the presumptive anterior and posterior ends of the cell, respectively. At this time, actin and the non-muscle myosin NMY-2 form a contractile network uniformly over the entire outermost layer, or cortex, of the embryo (Figure 1, left) (Munro et al., 2004). Polarization is blocked by actin inhibitors and myosin knockdowns, demonstrating the importance of actomyosin contractility for polarity establishment (Cowan and Hyman, 2007; Gonczy and Rose, 2005).

The sperm provides a polarity cue at the posterior end of the embryo that locally downregulates cortical contractility (Figure 1, second embryo) (Goldstein and Hird, 1996; Munro et al., 2004). The sperm pronucleus/centrosome complex closely associates with the posterior cortex, inducing local loss of the uniform NMY-2 network (Goldstein and Hird, 1996; Munro et al., 2004). This leads to contraction of the actomyosin cytoskeleton and flow of cortical material (cortical flow) away from the posterior signal, culminating in the strong anterior enrichment of actin foci and NMY-2 (Cowan and Hyman, 2007; Gonczy and Rose, 2005). As a consequence, the posterior cortex appears smooth and quiescent (i.e., with low contractility), while the anterior cortex remains highly contractile (Figure 1, third embryo).

The polarity signal acts at least partially through the negative regulation of the small G protein RHO-1. RHO-1 and the Rho guanine nucleotide exchange factor (GEF) ECT-2 (similar to the human Ect2 protooncogene) are essential for cortical contractility and for anterior enrichment of NMY-2 (Jenkins et al., 2006; Motegi and Sugimoto, 2006; Schonegg and Hyman, 2006). Through an unknown mechanism, the posterior cortex adjacent to the sperm centrosome becomes locally depleted of ECT-2, which presumably prevents the posterior activation and localization of RHO-1 (Motegi and Sugimoto, 2006). RHO-1 activity is also negatively regulated at the anterior by two partially redundant Rho GTPase-activating proteins (RhoGAP), RGA-3 and RGA-4 (Schmutz et al., 2007; Schonegg et al., 2007). Loss of these RhoGAPs leads to hypercontractility of the anterior cortex and

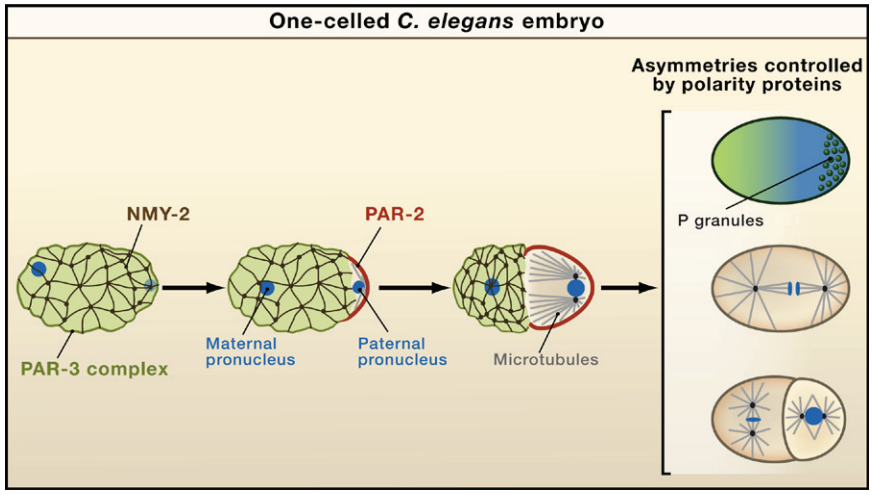

Figure 1. Polarity Induction and Transduction in the *C. elegans* Embryo

(Left) Before polarity induction, the actomyosin cortex (brown lines) is uniformly contractile. The PAR-3 complex (green), which contains PAR-3, PAR-6, and the atypical protein kinase C (aPKC), is distributed uniformly over the outermost layer, or cortex, of the oocyte.

(Middle) The polarity cue, dependent on the centrosome of the sperm and coincident with the growth of microtubules (gray lines), induces loss of actin and the nonmuscle myosin NMY-2 at the posterior of the embryo.

(Right) Movement of the actomyosin cytoskeleton to the anterior drives the PAR-3 complex to localize to the anterior. As the PAR-3 complex leaves, PAR-2 (red) associates with the smooth, quiescent posterior cortex.

(Far Right) PAR proteins control different polarized events in the daughter cells, such as cytoplasmic asymmetries (top), posterior placement of the mitotic spindle (middle), and cell-cycle timing differences in daughter cells (bottom).

excessive anterior movement of NMY-2. Because RHO-1 activates myosin contractility, positive regulation of NMY-2 by active RHO-1 at the anterior could cause anterior movement of the actomyosin cytoskeleton (Motegi and Sugimoto, 2006). Thus, both positive and negative regulation of RHO-1 are important for establishing the sizes of the contractile and quiescent domains.

The polarity cue is currently unknown, but it does depend on the sperm-donated centrosome: embryos with mutations that impair centrosome maturation or with centrosomes ablated by lasers both fail to polarize; further, the induction of polarity is coincident with the growth of microtubules from the centrosome (Cowan and Hyman, 2004; Cuenca et al., 2003; O'Connell et al., 2000; Wallenfang and Seydoux, 2000). Preventing the majority of microtubule growth from the centrosome by RNA interference (RNAi) of tubulin gene expression does not prevent polarity induction, indicating a large mitotic aster is not needed (Cowan and Hyman, 2004; Sonneville and Gönczy, 2004; Tsai and Ahringer, 2007). However, in embryos with low tubulin levels, polarity induction is delayed until a small aster forms, supporting a requirement for microtubules in the cue (Tsai and Ahringer, 2007). The sperm also appears to deliver to the posterior membrane CYK-4, a Rho family (e.g, Rho, Rac, or Cdc42) GAP (Jenkins et al., 2006). However, its relationship with RHO-1 is unclear because recent work suggests that CYK-4 acts on a Rac GTPase and not RHO-1 (Canman et al., 2008). No polarity phenotypes have yet been reported for Rac mutants, but as there are three *C. elegans* genes encoding Rac proteins, there could be redundancy.

The most important question remaining is the identity of the polarity cue and its mechanism of delivery and reception. One possibility is that microtubules locally deliver a signaling molecule to the cortex, such as a regulator that causes the removal or inhibition of the Rho GEF ECT-2. The current failure to find the polarity cue despite extensive RNAi and mutant screens suggests that redundant mechanisms could induce polarity. Indeed, Zonies et al. (2010) have very recently demonstrated the existence of two redundant pathways that polarize the *C. elegans* zygote, one depending on ECT-2 and the other on PAR-2. These new data combined with new approaches should help to identify the molecules involved.

A Link to Cytokinesis

It is striking that most of the regulators of cell polarity mentioned above are also involved in cytokinesis (i.e., the splitting of a cell into two cells during the late stages of mitosis) (Oegema and Hyman, 2006). This suggests that the embryo has co-opted the cytokinesis machinery for the establishment of polarity. During cytokinesis, actomyosin contractility is inhibited at the poles through cortical interactions with astral microtubules (Foe and von Dassow, 2008; Werner et al., 2007). Perhaps a similar mechanism involving the microtubules nucleated by the sperm causes local downregulation of actomyosin contractility during polarity induction. Given this relationship, it will be interesting to investigate possible roles for other cytokinesis players in polarity induction.

One important process in cytokinesis that has not yet been linked to the induction of polarity in *C. elegans* is lipid signaling. Recently, PPK-1, a PI(4)P-5-kinase that generates the phosphoinositide PIP_2, was found to accumulate at the posterior cortex near the sperm pronucleus approximately at the time of polarity induction (Panbianco et al., 2008). As PIP_2 is important for cytokinesis and regulates the activities of many actin-binding proteins, exploring the possible function of phosphoinositides in polarity induction might also be a fruitful topic of future research.

The PAR Proteins in *C. elegans*

A major consequence of asymmetric regulation of the actin cytoskeleton is the asymmetric localization of many of the PAR proteins and atypical protein kinase C (aPKC). Loss of any of these proteins disrupts cell polarity, usually resulting in two equal-sized cells that divide at the same time and have similar developmental fates (Cowan and Hyman, 2007; Gonczy and Rose, 2005). Asymmetric localization of PAR proteins occurs in two mechanistically distinct phases: establishment and then maintenance (Cuenca et al., 2003; Motegi and Sugimoto, 2006).

PAR-3, PAR-6, and the atypical protein kinase C PKC-3 (the PAR-3 complex) are initially localized uniformly at the cortex, but then they accumulate in the anterior of the cell after polarity induction (Cowan and Hyman, 2007; Gonczy and Rose,