Going with the Flow: An Elegant Model for Symmetry Breaking

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The entry of the sperm centrosome polarizes the anterior-posterior axis of the C. elegans zygote by inducing the formation of complementary cortical Par protein domains. Recent papers from the Seydoux and Grill laboratories (Goehring et al., 2011b and Motegi et al., 2011) reveal how two different symmetry-breaking mechanisms produce the same final pattern through interactions between Par proteins.

Cell polarity is critical for the form and function of almost all cell types and depends on a conserved network of cortical polarity proteins: a complex of Par-3, Par-6, and aPKC (Pkc-3 in C. elegans) defines one side of the cell and undergoes mutually antagonistic interactions with a second group of polarity factors, Par-1, Par-2, and Lgl, which define the opposite side. These Par (partitioning defective) proteins were originally identified in the C. elegans zygote, which provides one of the simplest and most tractable systems to investigate polarity (Goldstein and Macara, 2007). One important advantage of this system is that polarity is induced by the entry of the sperm centrosome at fertilization, allowing observation and manipulation of all steps of polarization, from the initial symmetry-breaking event to the final asymmetric cell division.

Prior to polarization, the entire cell cortex is occupied by the Par-3/Par-6/Pkc-3 complex. When the sperm centrosome or microtubule organizing center (MTOC) contacts the cortex, it triggers two visible changes. First, it induces contraction of the actomyosin cytoskeleton toward the anterior, which clears this anterior Par complex from the posterior (Cheeks et al., 2004; Munro et al., 2004). Second, it independently stimulates recruitment of Par-2 to the adjacent cortex, creating a posterior domain that gradually expands, even without cortical flows (Zonies et al., 2010). The final outcome of either event is a polarized cell with stable anterior and posterior cortical domains (Figure 1). Although the basic steps in these pathways are well understood, the mechanisms underlying this dynamic process have remained unclear. Two recent papers (Goehring et al., 2011b and Motegi et al., 2011) fill important gaps in our understanding of polarity induction in C. elegans, providing a more complete picture of how the axis is specified.

Motegi et al. studied the Par-2-dependent pathway in zygotes lacking cortical actomyosin flows. They observed that Par-2 associates with the MTOC and that the earliest cortical Par-2 correlates spatially and temporally with the arrival of the MTOC at the cortex. They find that Par-2 binds directly to microtubules in vitro, protecting it from Pkc-3 phosphorylation, which would inhibit its binding to phospholipids. Thus, microtubules from the MTOC could protect Par-2 from the Pkc-3 present throughout the cortex prior to polarization, allowing Par-2 to associate with the posterior plasma membrane. Supporting this, Par-2 mutants that cannot bind microtubules do not rescue polarity when cortical flows are absent but can rescue them when the actomyosin contraction removes Pkc-3 from the posterior.

Motegi et al. also addressed how the initial binding is stabilized once the sperm MTOC leaves the posterior cortex. They found that Par-2 at the membrane recruits Par-1, which phosphorylates Par-3 to exclude the anterior Par complex from the cortex. Furthermore, membrane-bound Par-2 recruits more Par-2, creating a positive feedback loop that expands the posterior domain. This paper therefore provides a simple and attractive explanation for symmetry breaking by microtubules, using just the interactions between Par proteins.

Goehring et al. (2011b) investigated the other symmetry-breaking system, which requires cortical contraction of the actomyosin network. Previous work showed that even in the absence of posterior Par proteins, Par-6 still transiently redistributes toward the anterior while cortical flows are active (Cuenca et al., 2003; Munro et al., 2004). Moreover, many proteins become transiently enriched in the anterior of the zygote during the early phase of the actomyosin contraction. It was unclear, however, whether the translocation of the anterior Par complex requires direct linkage to the actomyosin cortex. Goehring et al. addressed this question by modeling the cortex as a thin film of fluid, within which flows are induced by cytoskeletal contraction. They propose that the Par proteins are carried passively along with the flows—a process known as advection.

Their analysis is based on earlier quantitative measurements of the lateral diffusion of Par-6, its membrane dissociation rate, and cortical flow velocities in Par-2-depleted embryos (Goehring et al., 2011a). This earlier work demonstrated that targeting the anterior Par complex to the plasma membrane does not require the actomyosin cortex, ruling out a direct link between them. Using these measurements, Goehring et al. now calculated that cortical flows are sufficient to passively move the anterior Par complex in an advective current, and their modeling accurately reproduced the observed segregation pattern of Par-6.

Goehring et al. went on to address whether this transient asymmetry can induce the formation of stable Par domains. They built a model in which the anterior and posterior Par complexes antagonize each other’s association with the membrane so that their detachment rate depends on the local concentration of the opposing complex. This system produces...
multiple stable states: either an entirely anterior or posterior cortex or one with distinct anterior and posterior domains that persist despite unrestricted diffusion of Par complexes. Importantly, application of a sufficiently large perturbation can cause it to switch states. Subjecting such a system in the “anterior” state to cortical flows accurately reproduces the observed pattern of protein redistribution in polarizing embryos. The system reaches a similar polarized state in the absence of flows when triggered by local depletion of anterior factors from the posterior. However, the pattern evolves with different dynamics from those observed in wild-type embryos, supporting the idea that flows are the primary mechanism that induces polarity.

Finally, they addressed how the steady-state protein distribution is established and proposed that growth of each domain is constrained by depletion of a finite cytoplasmic pool of Par proteins. Consistent with this, increasing or decreasing the dose of either protein shifts the position of the steady-state boundary between Par-2 and Par-6. This stalling of domain growth due to the depletion of cytoplasmic pools explains why the positive feedback loop between Par-2 and Par-1 described by Motegi et al. does not expand the posterior domain until it covers the entire cortex. It also explains the earlier observation that par-2 mutants can be rescued by reducing the levels of the anterior Par proteins (Watts et al., 1996). Goehring et al.’s mathematical model for polarization of the C. elegans zygote therefore demonstrates that the known properties of the system are sufficient to account for all of the observed behaviors.

Together, these papers show how Par protein interactions establish and maintain the same stable, polarized state in response to different initial perturbations. This is important because other systems do not appear to use the same cues to induce polarity as the C. elegans zygote. Par-2 has no obvious orthologs outside nematodes, and there are currently no other examples of polarizing cortical contractions. The antagonistic interactions between the Par proteins are conserved; however, as Par-1 phosphorylates Drosophila Par-3 to exclude it from the cortex and aPKC phosphorylates Par-1 in both Drosophila and mammals to disrupt its association with the cortex (St Johnston and Ahringer, 2010). Thus, many polarized cells may use the same Par reaction-diffusion system to generate polarity from a variety of different initial perturbations.

REFERENCES


