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Cracking up: symmetry breaking in cellular systems

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The shape of animal cells is, to a large extent, determined by the cortical actin network that underlies the cell membrane. Because of the presence of myosin motors, the actin cortex is under tension, and local relaxation of this tension can result in cortical flows that lead to deformation and polarization of the cell. Cortex relaxation is often regulated by polarizing signals, but the cortex can also rupture and relax spontaneously. A similar tension-induced polarization is observed in actin gels growing around beads, and we propose that a common mechanism governs actin gel rupture in both systems.

Introduction

Cell polarization studies have unveiled many of the molecular pathways by which cells can break symmetry in response to asymmetric stimuli. The stimuli can be either intracellular, like during cytokinesis, in which the mitotic spindle induces the position of the cleavage furrow (Burgess and Chang, 2005), or extracellular, such as chemical gradients during chemotaxis (Chung et al., 2001). Interestingly, cells conserve the ability to polarize even in the absence of an asymmetric signal (Devreotes and Zigmond, 1988). Such spontaneous polarization could be caused by a biochemical instability generated by the amplification of small stochastic variations in polarity protein concentrations (Sohrmann and Peter, 2003; Wedlich-Soldner and Li, 2003). In many cases, however, symmetry breaking and polarization seem to be driven by a mechanical instability of the actomyosin cytoskeleton.

The cell membrane is supported by a thin cortical layer between 100 nm and 1 μm thick that consists of cross-linked actin filaments, myosin motors, and actin-binding proteins, the spatial organization and dynamics of which are only beginning to be resolved (Medalia et al., 2002; Bretschneider et al., 2004; Morone et al., 2006). The motors present in the cortex generate a contractile tension in the actin network (Dai et al., 1999) that can be relaxed if the cortex ruptures (Fig. 1 d). Local relaxation of the cortical tension can trigger polarization events such as global cortex flows (Bray and White, 1988; Munro et al., 2004) or the growth of membrane protrusions called blebs (Keller et al., 2002; Charras et al., 2005; Paluch et al., 2005). Similarly, during early neuronal differentiation, breaking of the neuronal sphere and sprouting of neurites seem to require local relaxations of the cortical actin meshwork, although, in this case, the role of myosin motors is unclear (Da Silva and Dotti, 2002). Polarization induced by a release of mechanical tension is also observed in simpler systems, such as in actin networks growing on beads that mimic *Listeria monocytogenes* motility. In this paper, we compare the biochemistry and the mechanics of polarization in cells and around beads, and we argue that the bead system can serve as a simple model system to study mechanically driven polarization in cells. Furthermore, we argue that both actin gels around beads and the actomyosin cortex in cells are close to an instability threshold. Instability can be triggered by an intracellular or extracellular signal or can occur spontaneously when a fluctuation exceeds the mechanical threshold. Finally, we discuss the likelihood that polarization, by locally overcoming a mechanical threshold, could apply more generally to a variety of biological systems.

Symmetry breaking around beads: an example of mechanically driven polarization

The mechanism by which cortical tension relaxes in cells is difficult to characterize because of the complexity of the cell. Mimicking the phenomenon under simplified conditions provides an alternative experimental way to study the mechanism of cortex breakage. An actin network that is mechanically comparable with the cell cortex is the actin gel that grows from the surface of a bead coated with an activator of actin polymerization (van der Gucht et al., 2005). Such beads have been used widely in the last 10 yr as a model system for studying actin-based movement of intracellular objects and lamellipodium extension (for review see Plastino and Sykes, 2005; Mogilner, 2006).

Beads (radii of 1–10 μm) are first covered with an activator of actin polymerization and are placed in cell extracts or in a mixture of purified proteins that reconstitutes the dynamics of actin-based movement observed for the bacterium *L. monocytogenes* (Bernheim-Groswasser et al., 2002). Actin polymerization is activated at the surface of the bead, and an actin gel grows outward in spherical geometry. During gel growth, new

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monomers are incorporated at the bead surface underneath the preexisting gel, which is thus pushed outward and stretched as a result of the curved surface (Noireaux et al., 2000). As a consequence, stresses build up, and the actin shell is under tension (Fig. 1 a). When this tension exceeds the maximum tension that the actin network can bear, the actin shell breaks, and the actin gel develops into a comet tail (Fig. 1 b; Sekimoto et al., 2004; van der Gucht et al., 2005). The gel rupture is most likely to take place in a region where the actin network is locally weaker. Interestingly, symmetry breaking does not necessarily occur at a single point in the actin gel; for large beads, under conditions in which gel growth is slow (e.g., at low gelsolin concentration), the gel may rupture at multiple locations, giving rise to several comets (Fig. 1 c; and unpublished data).

In some cases, the gel stops growing before the rupture threshold is reached. The stress in the gel is then below the critical value, and symmetry breaking is delayed. However, symmetry breaking may still occur if a local perturbation is induced in the gel or, for example, if a spontaneous fluctuation in the cross-linker density is large enough to bring the system over the threshold (van der Gucht et al., 2005).

Cortex instability and cell polarization

Like the actin layer that grows around beads, the cell cortex is a cross-linked actin meshwork under tension. Indeed, myosin motors exert contractile forces on the actin network (Dai et al., 1999). At a microscopic scale, the actin gels around the bead and the cell cortex appear to differ in several ways: the origin of the tension is different in the two systems, and the orientation of the actin filaments and the direction of network growth differ as well. However, at a mesoscopic scale, the two networks are very similar: both are cross-linked actin meshworks in which stresses develop tangentially to the actin layer (Fig. 1, a and d). Several aspects of the behavior of the gels growing around beads may therefore be reproduced in the cell cortex. Indeed, it has been proposed that just like the gel around beads, the cell cortex can rupture to relax the tension (Paluch et al., 2005). The relaxed region then expands as a result of pulling forces from the adjacent regions, which may lead to large cortical reorganizations and cell polarization (Fig. 1 d). By adding a bias with intracellular or extracellular cues, cells can use this cortical instability and the associated cortical flows in several ways.

For example, flows of the actomyosin cortex have been observed in various cell lines at the onset of cytokinesis, where they presumably contribute to cleavage furrow formation (Cao and Wang, 1990; DeBiasio et al., 1996). One mechanism that has been proposed to cause these cortical flows is a local relaxation of the cortex at the cell poles by astral microtubules (Fig. 2 a; Bray and White, 1988). However, this hypothesis remains controversial, as several experiments have shown that myosin can be recruited and activated in the equatorial zone even in the absence of cortex flows (Straight et al., 2003; Bement et al., 2005; Dean et al., 2005). It is well possible that the cell uses several redundant mechanisms and that direct myosin recruitment mediated by the spindle midzone and aster-triggered cortex flows both contribute to furrow positioning (Wang et al., 1993; Bringmann and Hyman, 2005). Another process that is

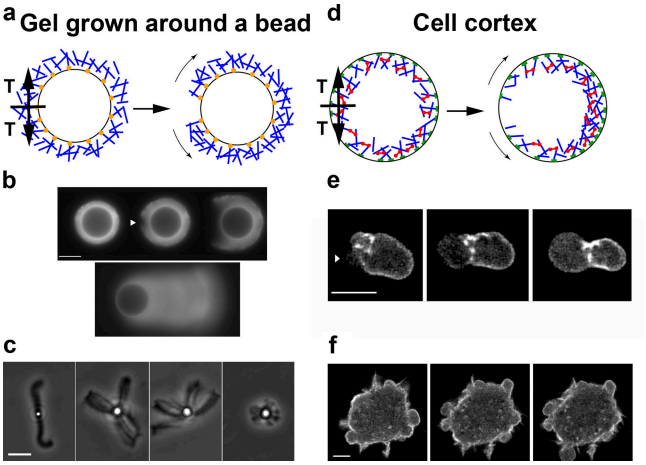

Figure 1. **Analogy of the tension state in an actin gel growing from a bead surface and in the cell cortex.** (a–c) Growing from a bead surface; (d–f) in the cell cortex. (a and d) Schematic view of the symmetry breaking of an actin gel growing from the surface of a bead (a) or the breakage of the cell cortex (d). Blue rods, actin filaments; red dumbbells, myosin fibers; green patches, membrane attachments; orange circles, actin polymerization activators. In both cases, a tension (T) builds up because of polymerization in curved geometry for the gel on the bead and because of the presence of myosin motors in the cortex. Rupture of the gel leads to actin shell or cortical movement (curved arrows). (b) Time lapse of a symmetry-breaking event (arrowhead) preceding the actin-based movement of a bead (epifluorescence microscopy with actin-AlexaFluor594). The first three images were taken 21, 24, and 40 min after the start of incubation, respectively. The last image shows the comet that develops eventually. Images are reprinted from van der Gucht et al. (2005) with permission from *Proc. Natl. Acad. Sci. USA*. (c) Phase-contrast images of beads of different diameters (1 μm for the left image and 2.8 μm for the three other images) at low gelsolin concentration. Images were provided by M. Courtois (Institut Curie, Paris, France). (e) Time lapse of cortex breakage (arrowhead) and bleb growth in an L929 fibroblast fragment expressing actin-GFP. Fluorescence images are projections from a three-dimension reconstruction (time between images is 20 s). Images are reprinted from Paluch et al. (2005) with permission from *Biophys. J.* (f) Time lapse of a cell displaying multiple blebs. Confocal images of an L929 fibroblast expressing actin-GFP were taken at 0, 25, and 35 s. Images were provided by J.-Y. Tinevez (Max Planck Institute of Molecular Cell Biology and Genetics, Dresden, Germany). Bars (b and c), 10 μm; (e and f), 5 μm.

thought to depend on local cortex relaxation is the polarization of the one-cell *Caenorhabditis elegans* embryo. Here, the sperm provides the external cue: after fertilization, the sperm centrosome moves toward the point of sperm entry, where it locally relaxes cortical contractility (Cowan and Hyman, 2004). As during cytokinesis, the cortex flows away from the relaxed region, transporting polarity proteins and shaping the pseudocleavage furrow (Fig. 2 b; Munro et al., 2004). Polarization by cortex relaxation may also precede cell migration in some cells (Paluch et al., 2006; Yoshida and Soldati, 2006).

In the aforementioned examples, cortex instabilities and polarization are triggered by a spatial cue that presumably relaxes the cortex locally. However, like the tension in actin gels grown around beads, the cortical tension can also relax spontaneously. For example, this is observed in cell blebbing (Fig. 1, e and f). Blebs are spherical bare membrane protrusions that are commonly observed during apoptosis (Mills et al., 1998), cell division (Burton and Taylor, 1997), cell migration (Sahai and Marshall, 2003; Yoshida and Soldati, 2006), and spreading (Bereiter-Hahn et al., 1990). Bleb formation is driven by the

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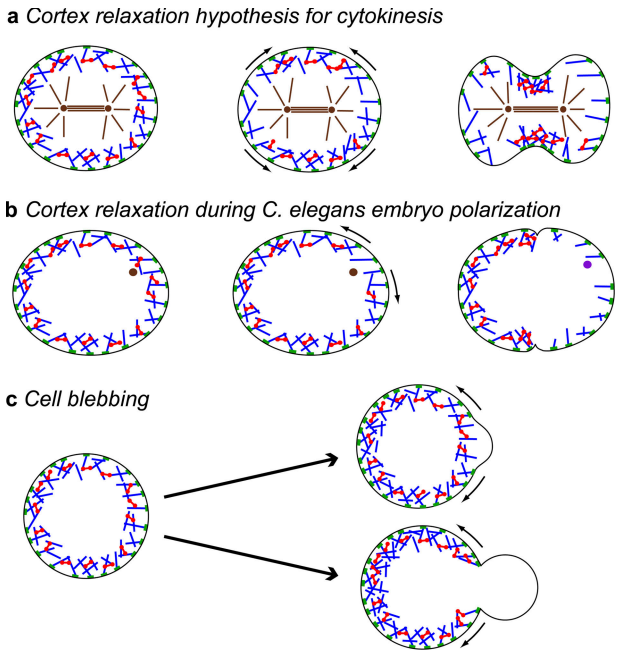

Figure 2. **Scheme for different cases of cortex relaxation in cellular events.** Blue rods, actin filaments; red dumbbells, myosin fibers; green patches, membrane attachments; brown rods, microtubules; brown dots, centrosomes. Curved arrows indicate the direction of cortex flows. (a) At the onset of cytokinesis, spindle microtubules have been proposed to cause cortex relaxation at the poles of the cell. The relaxed regions expand, leading to cleavage furrow formation. (b) In the *C. elegans* embryo, shortly after meiosis II, the sperm centrosome moves toward the site of sperm entry, where it triggers cortex relaxation. The cortex then flows away from the relaxed region, leading to polarity protein segregation and pseudocleavage furrow formation. (c) Blebs form at sites of local detachment of the membrane from the cortex (top) or at sites of local cortex rupture (bottom). Cortex detachment from the membrane is sometimes followed by local cortex disassembly at the base of the bleb (Charras et al., 2005). Note that under certain conditions, multiple blebs can form (see Discussion).

pressure generated by contraction of the actomyosin cortex and occurs in regions where the actin cortex is weakened. Blebs are thought to be initiated by rupture of the actomyosin cortex (Jungbluth et al., 1994; Keller et al., 2002; Paluch et al., 2005) or by detachment of the membrane from the cortex (Fig. 2 c; Charras et al., 2005; Sheetz et al., 2006). Interestingly, blebbing cells can form one single large bleb (Fig. 1 e; Paluch et al., 2005; Yoshida and Soldati, 2006) or multiple smaller blebs over the cell surface (Fig. 1 f; Cunningham, 1995; Charras et al., 2005).

A closer look at conditions under which symmetry breaks in cells or around beads

Symmetry breaking in gels around beads and cell polarization caused by cortex breakage or relaxation are both driven by a release of mechanical tension in the actin gel. Spontaneous rupture of the actin network occurs when the tension in the gel exceeds a threshold value that is determined by the strength of the network. If the tension is just below the threshold, symmetry breaking may still occur if a spontaneous fluctuation in the density of actin, myosin, or cross-linkers, for example, is able to bring the system locally over the threshold. This implies that symmetry breaking can be enhanced either by lowering the threshold (the strength of the network) or by increasing the global tension (the driving force). Observations of symmetry breaking in both the bead system and the cell cortex support this idea.

In both systems, the instability threshold can be lowered by lowering the density of cross-linkers in the actin gel, like filamin or α-actinin, which leads to a softer and weaker network. Indeed, the depletion of filamin or degradation of α-actinin in cells enhances blebbing, probably as a result of cortical breakage, or at least a local release in the cortical tension (Cunningham, 1995; Miyoshi et al., 1996). Conversely, shell breakage in the bead system is slowed down by the presence of filamin or α-actinin (van der Gucht et al., 2005). In both systems, actin gel rupture is thus facilitated by the depletion of cross-linkers.

The driving force for cortex breakage in cells can be enhanced by increasing the activity of myosin II, leading to an increased contractility of the cortex and a larger cortical tension. Indeed, blebbing in cells is enhanced when the global contractility of the cortex is increased (Sahai and Marshall, 2003), and, conversely, blebbing is reduced when contractility is decreased (Mills et al., 1998). In the bead system, the tension is related to the thickness of the gel layer. Thus, the analogous effect of decreased contractility (leading to a lower tension) in the bead system is a decrease in gel thickness. For example, this can be achieved by adding actin-depolymerizing factor/cofilin, which enhances the depolymerization of filaments in the outer regions of the actin gel. Indeed, at high actin-depolymerizing factor/cofilin concentrations, the gel thickness remains small, and no symmetry breaking is observed, indicating that the threshold tension for gel rupture can never be reached (van der Gucht et al., 2005).

A growing actin shell in spherical geometry can break spontaneously and form a propelling comet at the opposite side of the breakage point, although the original breakage and, thus, direction of the comet is random. If gel growth stops before the instability threshold is reached, symmetry breaking can still be triggered by an external perturbation (for example, by a local disruption of the actin network by photodamage; van der Gucht et al., 2005). Likewise, a local alteration of the actin cortex in cells, either by locally applying drugs that affect actin or by increasing the local stress mechanically, induces cortex rupture and bleb formation (Paluch et al., 2005).

We can compare the forces necessary for shell breakage around beads and for cortex breakage in cells. The stresses in the gel around beads can be estimated from the elastic modulus of the actin gel and the thickness of the gel (Noireaux et al., 2000). This produces a value of 10^3–10^4 Pa for the critical tensile stress for gel rupture (van der Gucht et al., 2005). The cell cortical tension has been estimated in different cell types and is on the order of 10^{-3} N/m for *Dictyostelium discoideum* (Pasternak et al., 1989; Dai et al., 1999), lymphocytes (Pasternak and Elson, 1985), or fibroblasts (Matzke et al., 2001), whereas it is ~20–30 times smaller for neutrophils (Evans and Yeung, 1989). With a cortical thickness of a few hundred nm, this provides a value of 10^3–10^4 Pa for the tensile stress in the cortex, which is very similar to the stress in the bead system. Interestingly, in *D. discoideum*, the deletion of either myosin II or of two myosins I

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leads to a decrease of the tension by ~50%, suggesting that most of the cortex tension is caused by myosin motors (Dai et al., 1999). Note that the cortical tension is very close to the threshold for cortex breakage, as breakage can be induced by applying pressures as small as 100 Pa, which is only 10% of the cortical stress (Paluch et al., 2005).

Symmetry can break from one point or from multiple points

Cortex instabilities can occur at multiple sites along the cell periphery, leading to multiple blebs, or it can be a single event leading to a global polarization of the cell (as during polarization of the *C. elegans* embryo or the formation of large blebs; Fig. 1, e and f). Similarly, the gel growing around a bead can rupture once, leading to the formation of a single comet tail, or it can break at multiple sites, leading to several comets (Fig. 1, b and c). The factors that determine whether a rupture leads to a global or to a local symmetry breaking are not well understood, but an analogy with polymerization reactions in chemistry or biology that proceed by nucleation and growth may provide insight. In such reactions, many short chains form if the generation of new polymer nuclei is fast compared with the growth of the polymers, whereas only a few very long chains are obtained if nucleation is slow compared with growth (Domb and Lebowitz, 1983). Similarly, if the nucleation of new holes in the stressed actin shell is fast compared with the growth of existing holes, the actin network is likely to break at multiple sites. In contrast, if nucleation is slow compared with the growth of a hole, the formation of a single hole will probably lead to global polarization. Indeed, multiple comet tails around beads are observed when gel growth proceeds slowly (e.g., at low gelsolin concentration; unpublished data) because there is more time for new holes to appear in the gel. The biochemical factors that regulate the nucleation and growth rates of holes in the cell cortex remain to be explored, but we can nevertheless speculate about factors that affect these rates. The nucleation rate in cells depends on how far the cortical tension is from the instability threshold. Obviously, in cases in which the spontaneous nucleation of instabilities does not occur but needs to be induced, there is usually only one rupture. On the other hand, in blebbing cells, nucleation is faster, and blebs form spontaneously and rapidly. Multiple blebs tend to form when cells adhere to the substrate (Cunningham, 1995; Sahai and Marshall, 2003), whereas one single large bleb is formed when cells are in suspension (Paluch et al., 2005). This might indicate that adhesion to the substrate could restrict membrane extension and, thus, bleb growth.

Stress-induced polarization in other systems

The concept of polarization driven by a global driving force that can locally exceed a mechanical threshold is not restricted to actin gels under tension but can be applied more generally. For example, in plant cells, fungi, or bacteria, the force that drives cell deformation and growth comes from the internal osmotic pressure, whereas the mechanical strength that resists deformation is provided by the cell wall. Because the pressure in the cell is homogeneous, the polarized growth of walled cells requires an inhomogeneous extensibility of the cell wall (Cosgrove, 2005). For example, root hairs and pollen tubes in plants and buds in budding yeast are all initiated as small bulges growing at the cell periphery in regions where the cell wall is locally softened (Harold, 2002). To achieve such a local wall softening, a cell needs to direct vesicles that contain cell wall–loosening enzymes to specific sites at the cell periphery. This directed transport requires a polarized cytoskeleton, which may, in turn, be achieved by a biochemical instability (Wedlich-Soldner and Li, 2003). Similarly, neuritogenesis starts by the growth of small buds at the initially spherical neuron surface. Buds are thought to result from pushing forces exerted by microtubules at spots where the actin network underlying the membrane is locally relaxed (Da Silva and Dotti, 2002). This relaxation could be tension driven because activation of the Rho–ROCK pathway, which activates myosin II, has been reported previously (Da Silva et al., 2003). It could also result from some other kind of instability triggered by external signals (Da Silva and Dotti, 2002).

On a larger scale, a mechanical instability has been proposed to explain the shape and size of oscillations observed during the regeneration of fresh water polyp *Hydra vulgaris*. At the initial stages, *H. vulgaris* cells form a hollow sphere consisting of a cell bilayer. This sphere inflates by the uptake of fluid and builds up pressure as a result of stretching of the cells, which is analogous to the accumulation of stress in the actin gel growing around a bead. It has been proposed that this stress is released by rupture of the cell layer followed by rapid shrinkage of the cell ball (Fütterer et al., 2003). Repeated cycles of growth followed by rupture and rapid shrinkage might be important for the first polarization step in *H. vulgaris* morphogenesis.

Concluding remarks

We have argued that the mechanical states of the actomyosin cell cortex and of actin gels growing from beads are comparable. Both actin networks are under tension, which can be released by breaking symmetry in answer to a cue or spontaneously. Both systems appear to be operating close to a mechanical threshold, which would increase their sensitivity to small stimuli but would also make the system sensitive to fluctuations.

Highly reactive systems operating close to instability thresholds may be frequently found in biology. A similar, although not mechanical, threshold mechanism is observed in budding yeast, for example, where Cdc42, a small GTPase, is required for bud formation. The expression of a constitutively active Cdc42 results in spontaneous polarization with random orientation (Lechler et al., 2001; Wedlich-Soldner et al., 2003). It is possible that the enhanced activity of Cdc42 brings the system closer to a chemical threshold, where it becomes sensitive to random fluctuations (Wedlich-Soldner and Li, 2003).

Comparing the forces necessary for rupture and the effects of various proteins on symmetry breaking suggests that the mechanisms of polarization of the cell cortex and of the rupture of gels growing around beads are very similar. As a consequence, understanding symmetry breaking in biomimetic systems may provide essential insight into spontaneous cortex

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rupture in cells. There are many open questions as to how exactly polarizing signals trigger the mechanical instability leading to cortex rupture. The centrosome–microtubule system plays an essential role here, but, to a large extent, the pathways by which it controls the cortex mechanics are still unknown.

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