Opinion TRENDS in Cell Biology Vol.15 No.11 November 2005

Cytokinesis series

The mechanism of cortical ingression during early cytokinesis: thinking beyond the contractile ring hypothesis

Yu-li Wang

University of Massachusetts Medical School, 377 Plantation Street, Suite 327, Worcester, MA 01605, USA

Owing to the rapid advances in genomic, proteomic and imaging technologies, the field of cytokinesis has seen rapid advances during the past decade. However, the basic model for the early stage of ingression, known as the contractile ring hypothesis, remains largely unchanged. From recent observations, it is becoming clear that early cytokinesis of animal cells involves a more extensive set of events, both temporally and spatially, than what is encompassed by the original contractile ring hypothesis. Activities relevant to cytokinesis, such as cortical contraction, can initiate well before onset of anaphase. Furthermore, equatorial ingression can involve multiple events in different regions of the cortex, including the establishment of anterior–posterior polarity, the modulation of cortical deformability, the expansion and compression of the cell cortex, and forces directed towards the interior of the cell or away from the equator. In this article (which is part of the *Cytokinesis* series), I evaluate critically key observations on when, where and how early ingression of animal cells takes place.

Introduction

Cytokinesis is now recognized as a complex, multistep process. The earliest sign of cytokinesis in animal cells typically appears several minutes after chromosomal separation, as membrane ingression along the plane previously occupied by the metaphase chromosomes. Despite recent advances in other aspects of cytokinesis, as has been discussed in this series, our understanding of the mechanism of early ingression has remained largely unchanged for decades. However, the current hypothesis is by no means conclusive and is inconsistent with several observations. As experimental results point to an increasingly complex picture, the contractile ring mechanism might have in fact limited the consideration of other equally plausible mechanisms. The purpose of this article is to examine carefully the existing observations and interpretation, with the hope of stimulating new experiments and alternative models. It will not attempt to replace the old dogma with a new one, but simply point to the stones that should not be left unturned during the coming age of investigation. Although membrane fusion and remodeling probably play a role in facilitating cleavage, these events are believed to dominate during later stages of cytokinesis and will not be addressed in this article.

Contractile ring hypothesis – is it the final word?

Current thinking regarding cytokinesis is dominated by the contractile ring hypothesis [1,2]. It describes a process initiated upon onset of anaphase, when signals mediated by microtubules induce dramatic restructuring of a cortical region that will eventually form the cleavage furrow [3]. Actin and myosin-II filaments first co-assemble into contractile bundles around the equator. Subsequent sliding of anti-parallel actin filaments, as a result of interactions with myosin-II, causes the bundles to shorten, much like the contraction of myofibrils. This tightening 'purse string' in turn causes the associated membrane to ingress. For the sake of simplicity, the furrowing region will be referred to as the equatorial region in the rest of this *Opinion* article, even though furrows are located away from the geometric equator in some divisions.

While there is indisputable evidence for the involvement of actin and myosin-II in cytokinesis in most divisions (reviewed in [2,4]), evidence for the contractile ring hypothesis is by no means conclusive. Key supporting evidence is as follows. First, membrane ingression is often accompanied by an increase in equatorial cortical rigidity, as detected by local membrane deformation in response to applied forces. These measurements were conducted at a scale of microns by sucking/poking the membrane-cortex with glass micromanipulation tools [4], and more recently at a scale of nanometers with atomic force microscopy [5]. The extent to which equatorial cortical rigidity is determined by local contractile activities is unclear; the increase in rigidity likely reflects the concentration and/or cross-linkage of proteins along the equator but might not be related to the contractile forces generated locally. Moreover, measurements of the flexibility of a dynamic cytoskeletal gel are affected by the rate of force application relative to the rates of polymer assembly–disassembly and crosslinkage–dissociation [6]. To measure cortical deformability relevant to cytokinesis, the probing process must be performed over a comparable time scale – over a period of

Corresponding author: Wang, Y-L. (yuli.wang@umassmed.edu).
Available online 4 October 2005

 0962-8924/$ - see front matter doi:10.1016/j.tcb.2005.09.006

seconds to minutes. This problem might explain some of the discrepancies in rheological measurements of the equatorial cortex [4].

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The second key observation is the presence of inward forces along the equator. In a classic experiment by Rappoport [7], a flexible microneedle parallel to the spindle axis was inserted through the pole and across the equatorial plane. A deepening furrow deflects the needle upon contact, indicating that the ingressing cortex is capable of exerting forces. A similar conclusion was reached by observing the deformation of oil droplets microinjected into the equatorial region [8]. However, while such deformation forces argue against a mechanism based primarily on membrane fusion, as in plant cytokinesis [9], they do not necessarily mean that forces are generated locally by a constricting ring. Instead, forces might be generated in several patterns, in or outside the equatorial region, and be transmitted through the cytoskeletal 'strings and rods' to the equator to cause probing needles to bend or oil droplets to deform.

Third, the concentration of actin, myosin-II and many other cytoskeletal and signaling proteins along the equator is usually viewed as evidence for a contracting ring (e.g. [10–12]). Although the disruption of the equatorial concentration of these proteins is often correlated with the inhibition of cytokinesis, most of these proteins perform multiple functions, and their concentrations along the equator might or might not be related to the generation of constriction forces. For example, the preprophase band of actin filaments along the equator of plant cells during early mitosis is believed to play a role in the specification of a division plane rather than the generation of constricting forces [9]. Moreover, the equatorial band of actin filaments is not readily detectable in some dividing cells [13,14]. The structure appears to be most prominent in cases where excessive forces are required for cleavage, such as the ventral cortex of adhesive cells [15], cells under compression [14] and the cortex of large embryos [11]. Therefore the equatorial band might represent a specialized structure, as either a means or consequence of boosting ingression forces or the membrane/cortical remodeling process.

Experiments with large embryos have provided additional evidence for the contractile ring hypothesis [4,16]. However, given the recent diverse results with various model systems, it seems risky to assume *a priori* that observations with large embryos will automatically apply to other cell types. Even for large embryos, the combined evidence supports the contractile ring hypothesis – but this is not unequivocal.

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Several alternative models of cortical ingression were proposed in the early 20th century [4], many of which have not been ruled out conclusively, particularly when one considers the possibility of multiple concurrent mechanisms to be discussed later. Some of these models might have received little attention because they are not as intuitive as the contractile ring hypothesis. However, they might be equally consistent with experimental observations and some might better explain specialized events such as the cellularization of *Drosophila* embryos or the highly asymmetric divisions of some embryos and oocytes [4,17]. Careful consideration of these old ideas could bring new insight into the ingression process.

When does cytokinesis start?

While it is crucial that cortical ingression takes place only after chromosomal separation, there is evidence that chemical and mechanical events associated with cytokinesis start substantially earlier. It is well known that most spread cells undergo retraction and rounding as they enter mitosis [18], reaching maximal rounding immediately before cytokinesis. Round embryos also show cortical contraction and stiffening across the entire surface during early mitosis, as detected by measuring the cell shape and deformation in responses to applied mechanical forces [4,19,20]. In addition, many proteins of the actin cytoskeleton show a global increase in cortical association during mitosis, well before the onset of cytokinesis [14,17,21]. In the fission yeast *Schizosaccharomyces pombe*, an equatorial band of poorly organized actin and myosin appears during prometaphase or metaphase, and this subsequently turns into a tight 'contractile ring' during anaphase [22,23]. Unlike ingression itself, these earlier cortical activities appear to be regulated by the local cyclin-dependent kinase activity instead of microtubules [20]. While they are often treated as events independent of cytokinesis, one must take into consideration that cytokinetic ingression does not take place entirely *de novo* during anaphase but in the context of a protein network preassembled and/or preconditioned throughout the cortex. It is possible that the main purpose of the ingression signal is to change the distribution pattern of forces, without necessarily increasing the total force output.

Where does early cytokinesis take place?

At least for several model systems, there is strong evidence that cytokinesis involves signals delivered by anaphase microtubules to the equatorial region [3,24–27]. While speculation has focused on the density of microtubules along the equator [28,29], negative results in several studies [30,31] suggest that it is probably the quality, not the quantity, of equatorial microtubules that is crucial for signaling.

A crucial question concerns downstream cortical events stimulated by upstream equatorial signals. An obvious possibility involves the induction of an equatorial concentration of signaling proteins, such as myosin light chain kinase that activates the myosin-II ATPase [32,33]. However, the equatorial concentration of cytoskeletal and signaling molecules varies considerably among cell types [13,14,34]. Even when these molecules or activities are visibly concentrated along the equator, the actual percentage in the furrow can be very limited [35].

For example, as much as 90% of myosin II molecules in a dividing *Dictyostelium* are localized outside the equatorial cortex [35]. However, equatorial signals might activate cytokinesis in a more subtle way than focusing the cortical contractility, by breaking the radial symmetry of the cortex and creating a gradient of contractile/rheological activities across the cortex.

Involvement of long-range coordination and anterior–posterior polarity

There is substantial evidence that cytokinesis involves not only activities along the equator but across the entire cortex. Global coordination among contractile, protrusive and rheological activities during cytokinesis was first suggested based on the relationship between cytokinesis and cell migration. For animal cells capable of migration, cytokinesis is coupled to the establishment of a global anterior–posterior polarity while the two daughter cells move away from each other [36], with the cleavage furrow being equivalent to the posterior region of a migrating cell. Long-range, retrograde cortical flow of actin and associated membrane components takes place during both cell migration and division, driving a similar set of proteins towards the tail in migrating cells and to the cleavage furrow in dividing cells [36–38]. Furthermore, as actin assembly at the leading edge is believed to supply the filaments for cortical flow [39], *de novo* assembly of actin at polar regions might be essential for cytokinesis and could account for the sensitivity of cytokinesis to agents that inhibit actin polymerization [40].

In *Dictyostelium*, this cell migration/traction-driven process is sufficient to cause cleavage on adhesive substrates in the absence of myosin II [41,42]. Although it is often viewed as an alternative mechanism specific for adherent, migrating cells, at least some aspects of this mechanism, such as the establishment of anterior–posterior polarity and the generation of ripping forces, might play a general role in cytokinesis (discussed later) [42]. In addition, as this myosin-II-independent, traction-driven ingression takes place at the right time and place in *Dictyostelium* [41,42], signals for cytokinesis must be able to regulate activities in addition to, or other than, myosin-II motor activities.

This connection between cytokinesis and cell migration received fresh attention recently, with the observation that phosphoinositide 3-kinase (PI3K) is localized preferentially in the polar region, while PTEN, the phosphatase that reverses the action of PI3K, is concentrated at the cleavage furrow of *Dictyostelium* [43]. In addition, *Dictyostelium* cells lacking PI3K and/or PTEN fail cytokinesis in suspension and on substrates [43]. PI3K is a key enzyme for the anterior region of a migrating cell, whereas PTEN plays a role in promoting the formation of the tail [44]. Their differential distribution in interphase cells appears to be established through a global mechanism dependent on small GTPases [45], which have been shown to regulate cell rounding during division [18]. It will be important to determine whether similar gradients of localization occur in dividing animal cells and particularly in nonmigrating cells such as early embryos and whether they play a role in defining the location and/or timing of cortical ingression. However, as PTEN is defective in many transformed cells that divide vigorously [46], either its role in mammalian cytokinesis is more complicated than what is implied in *Dictyostelium* or its function in cytokinesis is abolished during oncogenic transformation.

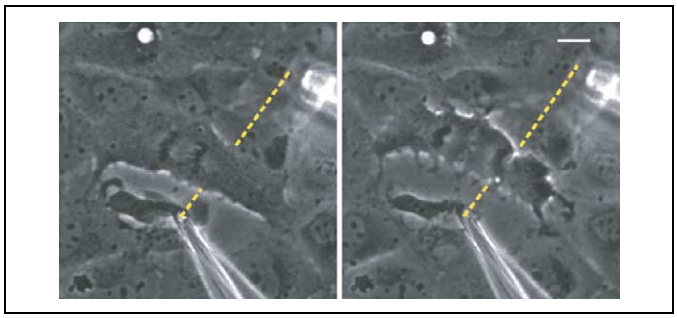

Figure 1. Ectopic furrow induced by a line of cytochalasin D. A pair of release needle (lower middle) and suction needle (top right) was used to apply 5 μM cytochalasin D to an NRK cell along a narrow line. The treatment causes inhibition of cytokinesis along the equator and formation of a pseudo-furrow along the line of drug distribution (dotted lines). Regions flanking the equator show an increase in phase density. Some global changes in cell shape complicate the interpretation for some cells, but not in this case. Bar, 10 μm.

Involvement of the polar cortex

Direct evidence for the involvement of the polar cortex in regulating the site of early cytokinesis came from local application of drugs acting against the actin cytoskeleton. Surprisingly, local release of cytochalasin D near the equator not only fails to inhibit cytokinesis but appears to increase the rate of ingression [47]. Conversely, release of cytochalasin D near the spindle pole causes inhibition of cytokinesis. In addition, application of a thin line of cytochalasin D outside the equatorial region is sufficient to induce ectopic ingression in some cells, although it is not sufficient to cause complete cytokinesis (Figure 1). These results strongly suggest that the integrity of a wide area of the cortex is required for equatorial ingression. As cytochalasins bind to the plus-ends of actin filaments *in vitro* [48] and weaken cortical rigidity without causing net actin depolymerization *in vivo* [49,50], they might promote ingression by increasing the deformability of the equatorial cortex (discussed later) or by facilitating cortical remodeling, as during exocytosis [51].

Involvement of the subcortical cytoskeleton

Cytokinesis might involve not only contractions of the cortical layer but also interactions between the cortex and the subcortex cytoplasm. The dominant role of the cortex is demonstrated by the lack of effect when interior cytoplasm on the cleavage plane is disrupted with a microneedle [4,52], and by the presence of a conspicuous equatorial actin-rich cortex [1]. However, these experiments do not rule out the involvement of the subcortical cytoskeleton in the generation of cleavage forces. Reconstruction of optical sections of cultured cells indicates that actin and myosin filaments are present not only on the cortex but also deeper, in the central region of the equatorial plane, throughout cytokinesis [15,38]. These actin filaments are oriented along the spindle axis or associated end-on with the membrane, sometimes with

a morphology akin to that of stress fibers [15,53]. End-on filaments are expected to generate force components perpendicular to the membrane plane and to allow a direct mechanism for ingression (discussed below). In addition, forces along the spindle axis might facilitate cytokinesis by pulling daughter cells away from each other (discussed below) and possibly by pulling cytoplasm away from the equatorial region.

How does early cytokinesis take place?

From a mechanical point of view, equatorial ingression could be driven not necessarily by a local increase in forces but by a shift in the balance between active forces and passive resistance along the equator. Mechanical forces that affect ingression include inward constriction or contraction forces, hydrostatic pressure in the cytoplasm and elastic forces of the cortex controlled by the concentration, binding stability or crosslinking activities of structural proteins. While the contractile ring hypothesis emphasizes a local increase in constriction forces, ingression might be driven equally effectively by changing any factor that shifts the balance among these mechanical elements.

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Cortical sinking mechanism

Other than a constricting ring, what else might cause equatorial ingression? First, if actin filaments are associated plus-end-on with the membrane, interactions with myosin-II would generate force components perpendicular to the membrane. Such sinking forces would work equally well for both conventional cytokinesis and special cases such as cellularization and highly asymmetric divisions. The forces might be generated by a filament sliding mechanism similar to the contractile ring, with one end of a bundle anchored to the membrane and the other end to a subcortical structure or by anchoring myosin II to a subcortical structure such as anillin [54] while pulling on membrane-associated actin filaments. The latter mechanism is supported by the actin-independent assembly and organization of myosin-II in sea urchin embryos and in fission yeast [55,56].

Cortical ripping mechanism

Based on the relationship between cytokinesis and cell migration as discussed above, one would expect the two daughter cells to exert opposite forces to the equatorial region and tear the cell apart (Figure 2 and Figure 3c). This mechanism is supported by the orientation of a set of actin filaments along the spindle axis [15]. In one scenario, adherent cells exert strong, opposite traction forces on the substrate underneath polar regions (Figure 2) (M. Murato-Hori, M. Dembo and Y-L. Wang, unpublished) [57,58]). Counter-forces exerted by the substrate on the dividing cell would point away from the equator and rip the daughter cells apart (red arrows, Figure 3c). However, this mechanism does not necessarily require substrate adhesion. A similar mechanism for non-adhesive cells could involve an array of actin filament bundles anchored at one end to the equator and the other end over a wide region outside the equator (green fibers, Figure 4a). This organization would focus contractile forces along the equator (green arrows, Figure 4a) and generate net ingressive forces (red arrows, Figure 4a). Although cortical ripping represents a direct, effective mechanism for cleavage, it is unable to generate the equatorial orientation of actin filaments seen in many dividing cells and is unlikely to be the sole cleavage mechanism in most dividing cells.

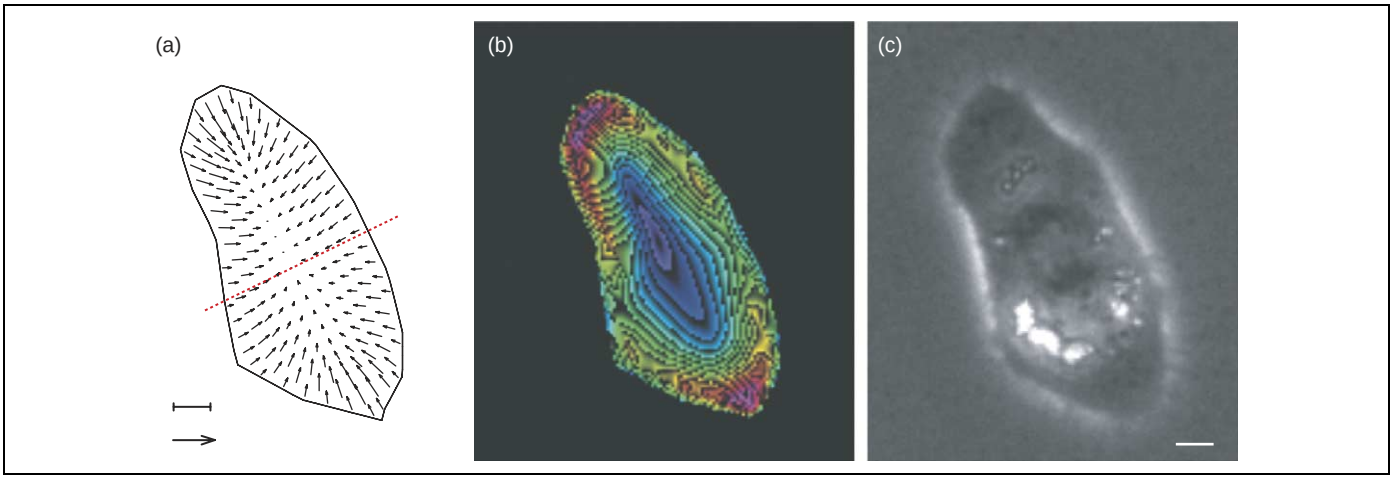

Figure 2. Distribution of traction stress underneath a typical NRK cell during the earliest stage of cytokinesis. Traction forces are detected by plating cells on flexible polyacrylamide substrates embedded with fluorescent particles. Deformation of the substrate was measured based on particle movements, and the data obtained used for computing the distribution of traction stress (forces per unit area) with the LIBTRC package (M. Dembo, Boston University, USA). The length and direction of arrows in **(a)** indicate the magnitude and direction, respectively, of traction stress exerted by the cell on the substrate. Centripetal forces are detected around the entire cell periphery but are stronger at the two poles. Counter-forces exerted by the substrate on the cell would point in opposite directions, away from the equator and pull the daughter cells away from each other. The dotted line indicates the equator. Panel **(b)** shows the magnitude of traction stress rendered in colors, with red representing strong forces. Panel **(c)** shows the corresponding phase-contrast image. Arrow scale bar in (a): 3.33×10^{4} dyn cm^{-2}; bar in (c), 4.1 μm.

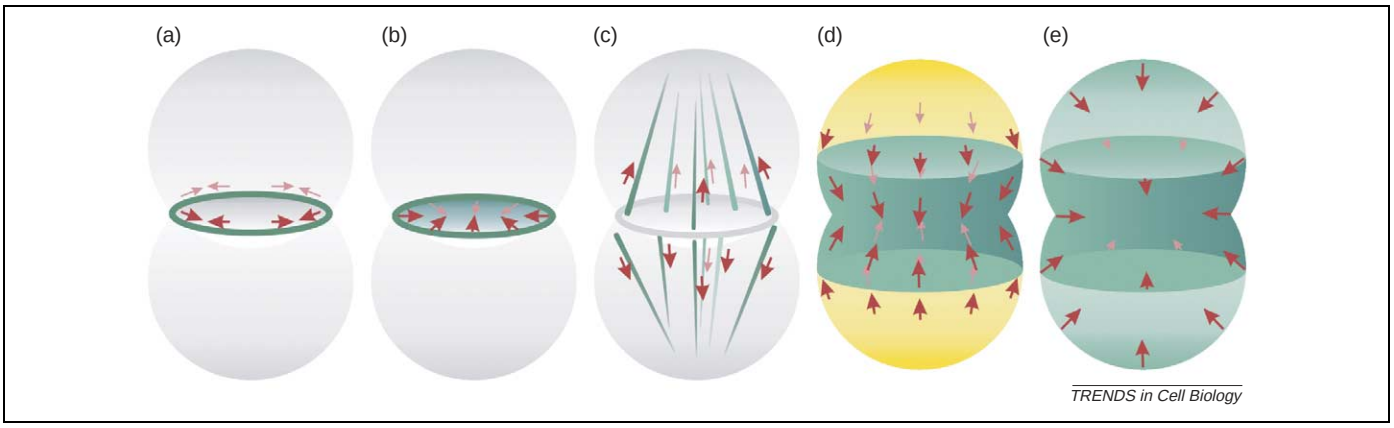

Figure 3. Possible mechanisms of ingression during cytokinesis. It should be emphasized that these mechanisms are not necessarily mutually exclusive and that cell division might involve several mechanisms simultaneously. **(a)** contractile ring; **(b)** cortical sinking; **(c)** cortical ripping; **(d)** polar expansion–equatorial compression; **(e)** global contraction–equatorial deformation. Red arrows indicate the direction of forces. Green indicates areas of contraction. Dark green areas in (d) and (e) indicate the 'crumple zone'. Yellow in (d) indicates regions of net cortical expansion.

Polar relaxation and polar expansion–equatorial compression mechanisms

The alternative to the contractile ring hypothesis that has received most attention is the polar relaxation hypothesis. It proposes that the primary target of cytokinetic signals is the polar cortex, which relaxes upon stimulation, whereas other regions of the cortex are maintained in a contracting state, causing the cortex to ingress along the equator [59,60]. Although there is convincing evidence against a narrowly defined polar relaxation hypothesis [24], some elements of the hypothesis such as the involvement of a globally active cortex appear compatible with the spatial and temporal considerations discussed above. One possibility involves a 'crumple zone' along the equatorial region, triggered by the anaphase ingression signal. For example, He and Dembo proposed a mechanism based on differential expansion between the equatorial and polar cortices [61]. The mitotic cortex is hypothesized to be in a globally expanding state constrained by a finite cell volume, until anaphase onset when a signal along the equatorial region decreases its expansion activity. The balance of forces then causes the polar cortex to undergo net expansion (yellow regions, Figure 3d) and the equatorial cortex to undergo net shrinkage (green regions, Figure 3d), which in turn compresses the equatorial cortex and causes cortical actin and myosin filaments to organize along the equator into a constricting ring (Figure 3d) [61]. However, while mathematical modeling of this mechanism has generated realistic shapes of dividing embryos, a mechanism for cortical expansion in dividing cells remains to be demonstrated. In addition, recent studies indicate that an equatorial orientation of filaments can take place without the forces of myosin II, inconsistent with a force-dependent mechanism suggested by this and other polar relaxation theories [60,61].

Global contraction–equatorial deformation mechanism

Alternatively, a dividing cell might generate inward compressive forces over the entire cortex during metaphase. This inward force (red arrows, Figure 3e, and green arrows, Figure 4b) is resisted by the outward elastic force of the cortical cytoskeleton (purple arrows, Figure 4b)

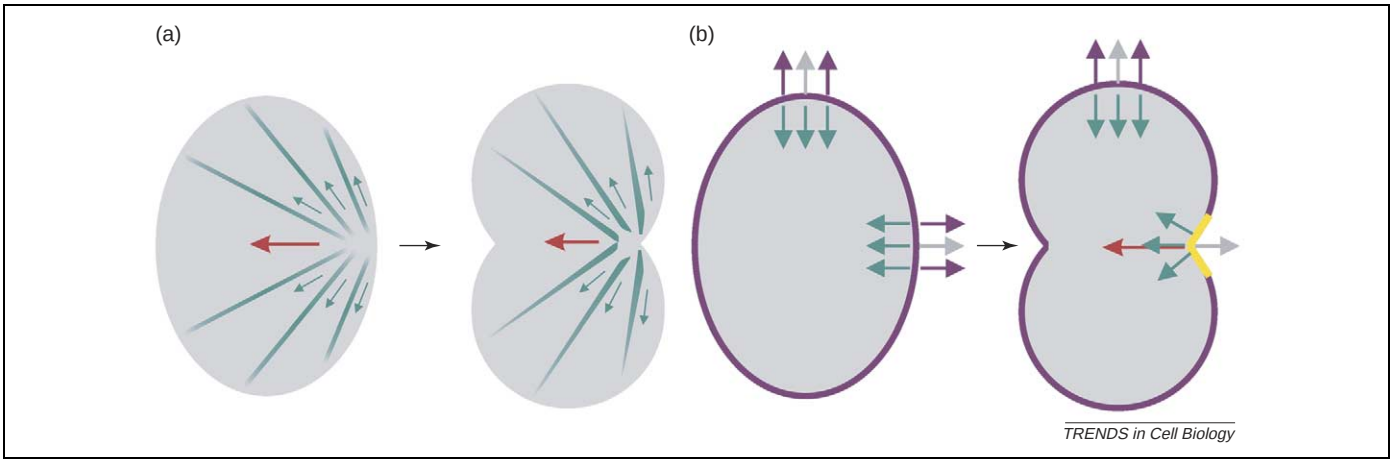

Figure 4. Forces in the cortical ripping [**(a)**, Figure 3c] and global contraction–equatorial deformation [**(b)**, Figure 3e] models. In the cortical ripping model (a), the distal end of the contractile fiber is anchored to either a rigid polar cortex or directly or indirectly to the substrate. The proximal end is attached to the equatorial cortex. Contractile forces concentrated along the equator (green arrows) create net ingression forces (red arrows). Note that, as long as the distal end of contractile fibers is anchored to a rigid cortex, this model does not necessarily require substrate adhesion. In the global contraction–equatorial deformation model (b), global contractile forces of the cortex (green arrows) are initially balanced by the hydrostatic pressure (gray arrows) and the elastic forces of the cortex (purple arrows). Cytokinetic signals cause the equatorial cortex to become more flexible (yellow outline), thus decreasing its elastic forces. This creates net inward forces along the equator (red arrow) and initiates the ingression. For the sake of clarity, forces are indicated only on one side of the equatorial cortex.

and the hydrostatic pressure in the cytoplasm (gray arrows, Figure 4b). Cytokinetic signals at the onset of anaphase cause the equatorial region to become more deformable (green region, Figure 3e, and yellow outline, Figure 4b), thereby weakening elastic forces and generating a net inward force to initiate the cortical collapse (red arrow, Figure 4b) [62,63]. This model predicts that the primary effect of the equatorial signal is to increase equatorial cortical deformability, as suggested by the local application of cytochalasin D described above. As for the contractile ring hypothesis, sustained ingression is likely to involve continuous modifications of cortical structure, rigidity and/or contractile forces.

Involvement of structural assembly and turnover

Structural dynamics have to be taken into consideration when hypothesizing ingression mechanisms. For example, a contractile ring might be expected to have a higher degree of structural stability, as for myofibrils, than a deformation-driven cortex that emphasizes structural remodeling. Disassembly of the equatorial cortex was recognized decades ago in an insightful analysis of electron micrographs [64], where the thickness of the cortex was shown to remain constant during early cytokinesis despite the decrease in equatorial radius, which would otherwise cause an increase in cortical thickness. A similar observation was made subsequently with fission yeast [23]. Recent FRAP analyses further indicated an unusually high rate of structural turnover along the equator [40,65,66], supporting the idea that proteins are continuously transported into and disassembled from the equatorial region to allow remodeling. Two recent studies, using the nonmuscle myosin-II inhibitor blebbistatin [67], suggested that the ATPase activity of myosin-II is required for the turnover of cortical actin filaments [65,66]. These results raise the possibility that equatorial myosin-II not only provides the contraction forces but also drives turnover of actin filaments along the equator to allow ingression to take place. However, as adhesive myosin-II-null cells are able to divide along the equatorial plane, remodeling of the cortex likely includes additional mechanisms [41,42].

Finally, is the equatorial organization of actin and myosin filaments an active assembly process [40] or a passive consequence of contraction [41,42]? Cells treated with blebbistatin show an apparently normal organization of equatorial actin and myosin-II despite the total inhibition of cytokinesis [65–67], arguing against a passive contraction/ingression-dependent mechanism [60]. However, it is possible that the organization might be driven by a myosin-II-independent mechanism such as microtubule motors, without net assembly along the equator.

The multiple facets of cytokinesis – cell-specific versus universal mechanisms?

Cytokinesis is characterized by an intriguing mixture of conserved and cell-type-specific features. The former includes the involvement of actin filaments, equatorial signals and coordination with chromosomal separation; the latter includes the organization of equatorial cortex and the involvement of cell adhesion and migration. It is clear that a simple, universal contractile ring hypothesis is untenable; however, it also appears unlikely that each cell type employs a unique mechanism of cleavage.

From studies with a wide range of model organisms, what emerges is that cytokinesis, like interphase, is not a single event but a collection of events that take place simultaneously towards the end of cell division. Many of them affect force balance along the equator to promote cleavage in different ways, but none of them can be viewed as the sole defining event of cytokinesis, as different cell types or organisms might employ different combinations of events – for example (X, Y, Z) versus (X, Z) or (Y), where X, Y and Z are events during cytokinesis. A somewhat different but equally plausible view is that different cell types use the same set of mechanisms, with both conserved and diverse features – for example (X, Y, Z) versus (X′, Y′, Z′) or (X, Y′, Z′). The two views might affect how one handles model systems as the latter emphasizes searching for common denominators, whereas the former emphasizes selecting optimal model systems for the dissection of specific events.

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Concluding remarks

Much of the current effort has focused on the acquisition of an inventory of molecules for cytokinesis, using approaches such as genetics [68], RNAi-based gene silencing [69] and proteomics [70]. While the information is essential for a thorough understanding of cytokinesis, the complexity of the outcome suggests that these screens might not be directed at a single mechanism but several mechanisms that span a wide spatial and temporal range and share a common, crude phenotype – failure of cleavage. It would be helpful to refine the experimental strategy to target future studies at specific events during cytokinesis. In addition, it is essential to put these observations in proper perspective when applying them to species far across the phylogenetic tree, particularly if different cell types use different combinations of mechanisms, as discussed above.

In addition to genetic and molecular screens, a major challenge will be to develop experimental tools that determine the functional states of cytoskeletal or signaling proteins at a high spatial and temporal resolution. As cell division is a mechanical phenomenon, it is doubtful that thorough understanding can be reached by probing only protein–protein interactions without understanding the physical consequences. Thus, in addition to probes for signal transduction and protein–protein interactions [34,71], it will be equally important to develop methods that detect the activities of motor proteins, the rheological properties of the cytoplasm [72], and the distribution of mechanical forces both on the cortex and within the cell. Equally useful will be approaches that perturb functions at a high spatial and temporal resolution, including localized release of inhibitors [47], localized activation of

enzymes or motor proteins [73] and photo-ablation of specific structures [74]. The combination of classical micromanipulative approaches with modern imaging and molecular manipulations holds particularly interesting potential [75].

Finally, while the contractile ring hypothesis might be acceptable without quantitative analysis, mathematical modeling represents an essential passport for crossing the border between biology and mechanics, and particularly for evaluating alternative, less-intuitive ingression models [61,76]. Most useful would be models capable of integrating multiple interacting processes and generating experimentally verifiable phenotypes such as the shapes and kinetics of ingression. They will likely provide new insights by allowing direct comparisons between experimental measurements and mathematical models and by generating aberrant behaviors through systematic variations of modeling parameters for comparisons with molecular/pharmacological manipulations.

Acknowledgements

I thank Micah Dembo for stimulating discussions, Maki Hori and Micah Dembo for providing the traction force results, Anne Warner for performing the experiment on linear cytochalasin release, and Mian Zhou for reading the manuscript. I would like to acknowledge in particular the excellent comments provided by five reviewers and the *TCB* editor, which have greatly improved the balance of the presentation. My research is supported by NIH grant GM-32476.

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