Force to Divide: Structural and Mechanical Requirements for Actomyosin Ring Contraction

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ABSTRACT One of the unresolved questions in the field of cell division is how the actomyosin cytoskeleton remains structurally organized while generating the contractile force to divide one cell into two. In analogy to the actomyosin-based force production mechanism in striated muscle, it was originally proposed that contractile stress in the actomyosin ring is generated via a sliding filament mechanism within an organized sarcomere-like array. However, over the last 30 years, ultrastructural and functional studies have noted important distinctions between cytokinetic structures in dividing cells and muscle sarcomeres. Myosin-II motor activity is not always required, and there is evidence that actin depolymerization contributes to contraction. In this Review, the architecture and contractile dynamics of the actomyosin ring at the cell division plane will be discussed. We will report the interdisciplinary advances in the field as well as their integration into a mechanistic understanding of contraction in cell division and in other biological processes that rely on an actomyosin-based force-generating system.

INTRODUCTION

The actomyosin ring is a transient structure essential for contractile force generation in animal and yeast cell division (1,2). Rappaport (3) and Schroeder (4) originally described the mechanics and biochemical makeup of the actomyosin ring. The bending of a microneedle inserted into the cleavage furrow of a dividing echinoderm egg provided the first evidence of force production large enough to allow cytokinesis (3) while the first electron micrographs of the cleavage furrow revealed a continuous ring (Fig. 1 *A*, *top*) built of actin and myosin-II filaments aligned along the division plane (4,5). Resembling the organization of actin and myosin-II filaments in the striated muscle, actomyosin structures in cell division were thought to operate similarly to sarcomere units, relying on the activity of myosin-II motor as the main force-generating element in a highly organized antiparallel actin filament array (Fig. 1 *A*, *bottom*). Myosin-II motor acts as a mechanoenzyme by using cycles of ATP hydrolysis (~100 pN × nm per cycle) to drive actin filament translocation in a directional power-stroke mechanism toward the barbed end of the actin filaments (6,7). Single molecule experiments show that the myosin head working stroke is completed within 5 ms and produces a filament shift of ~5 nm (8). During filament sliding, the work of the motor (applied force × step size) cannot exceed a fraction (tens of pN × nm) of energy produced by ATP hydrolysis, thus the working stroke generates a force of a few pN followed by motor detachment from the actin filaments (9) due to the nonprocessive nature of myosin-II (10,11).

Over the years, notable distinctions have been observed despite the expected similarity between actomyosin structures in muscle sarcomeres and contractile rings. In contrast to the conservation of mass observed in cycles of contraction and relaxation of the striated muscle, one of the most striking differences is the loss of mass during actomyosin ring ingression in cell division (5). Additionally, the contractile ring was reported as a dense and highly dynamic actin meshwork (12–15). GFP-actin fluorescence recovery analysis in photobleached cleavage furrow of pig kidney epithelial cells shows an average turnover time of 26 s (15). Ultrastructural analysis of *Schizosaccharomyces pombe* contractile rings shows that actin filaments assume mostly random orientations along the ring rather than forming highly organized sarcomere-like arrays (16). Moreover, experimental evidences in *Saccharomyces cerevisiae*, *Dictyostelium discoideum*, and vertebrates on the ability of cells to divide in the absence of or with impaired myosin-II motors suggest the existence of alternative force-generating mechanisms (17–20).

How is it possible for a random filament orientation to always generate contraction or for contraction to be possible in the absence of the myosin-II motor? Interdisciplinary advances in experimental findings and biophysical models describing different possible mechanisms for the contraction of actomyosin ring structures in cell division will be described.

ARCHITECTURE OF ACTOMYOSIN CONTRACTILE STRUCTURES AND ITS IMPLICATION ON THE MECHANISM OF CONTRACTION

The distribution of actin filaments in actomyosin contractile structures can be characterized by two main parameters:

1. Orientation of actin filaments relative to the equatorial plane; and

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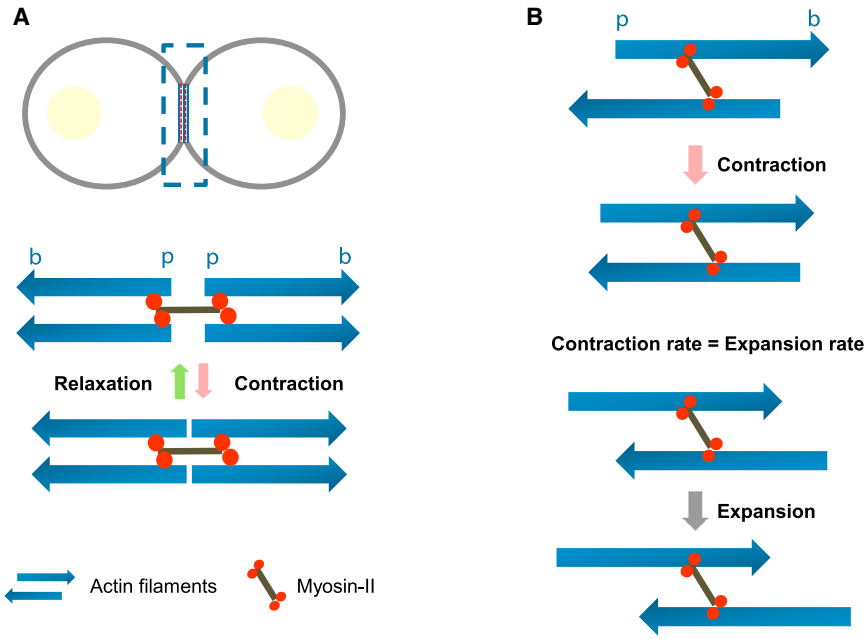

FIGURE 1 Actin and myosin-II filament distribution along the cytokinetic ring. (*A*, *upper panel*) Illustration of a cell with an actomyosin filamentous ring (inside the *dashed rectangle*). (*A*, *lower panel*) Sliding of actin filaments by myosin-II motor produces contraction of actin filaments organized in a sarcomere-like organization. (*B*) Myosin-II motor operates in a contracting (*top*) and expanding (*bottom*) configuration with antiparallel actin filaments. Myosin-II motor sliding produces equal rates of contraction and expansion. (*Arrowheads*) Barbed end of the actin filaments. (*b*) Barbed and (*p*) pointed actin filament ends.

2. Filament polarity with respect to the neighboring filaments.

In the muscle sarcomere, all filaments orient along a line with polarities of the adjacent filaments opposite of one another, hence the filaments are antiparallel. This ordered antiparallel filament structure makes it possible for the sarcomere to contract under the action of force generated by myosin-II thick filaments (Fig. 1 *A*, *bottom*).

Although actomyosin ring architecture has been classically associated with the muscle sarcomere, different ultrastructural studies have reported two other types of ring microstructure: gel-like and random one-dimensional structures. The gel-like ring is comprised of uniformly distributed actin filaments randomly oriented with respect to the cell cleavage plane. In this structure, the polarity of actin filaments is also isotropic. The random one-dimensional ring consists of overlapping filaments aligned parallel to the equatorial line in the cleavage plane, but filament polarity along the ring is random so that in any ring cross-section, both parallel and antiparallel neighboring filaments can be observed.

The gel-like structure has been observed in contractile rings of HeLa and *D. discoideum* cells (12,14) with short actin filaments with an average size of 100 nm. All dimensions (perimeter, width, and thickness) of the ring appear to be larger than the reported filaments' average length. As such, ring architecture strongly differs from an ordered one-dimensional sarcomere structure, and both qualitative and quantitative descriptions of ring contractility must invoke novel biophysical approaches. The models for contraction dynamics of these structures consider the actomyosin ring as a two- or three-dimensional meshwork of actin filaments crosslinked by myosin-II motors (21,22).

In the 1970s, it was originally reported that in organisms including jellyfish (4), sea urchin (5), squid (23), and *Xenopus* (24), the actin filaments in the contractile ring are oriented along the cleavage plane. Similar organization of actin filaments was observed in locomoting heart fibroblasts with the length of filamented actin in the range 2.5–13 μm (25). Determined mostly by cell size, the rings have variable initial diameter and width (the dimension along the spindle axis); however, the thickness of the ring (measured in the direction of the ring radius) has been observed in the range of 100–400 nm (26). Although the average size of actin filaments also varies, it generally appears to be larger than the ring thickness. For example, in the fission yeast contractile ring the average filament size is 600 nm while the ring thickness is ~200 nm (16). Long actin filaments can buckle and bend, but as the curvature radius of bent filament decreases to ~300 nm, it becomes prone to severing (27). Thus, the relation between the average size of the actin filaments and the ring thickness might be a reason the gel-like ring structure is not observed in these and other organisms.

There is little knowledge about the orientation and polarity of overlapping actin filaments along the longitudinal section of a ring. However, electron microscopy reconstruction of the fission yeast cytokinetic ring reveals two oppositely oriented bundles of parallel filaments, progressively evolving into a random one-dimensional structure in late anaphase (16). A similar random one-dimensional structure of actin filaments exists in motile fibroblasts (25). Although many attempted to explain the contraction mechanism of a ring with random polarity of actin filaments, the

mechanisms remained elusive until recently. Below, we discuss two key mechanisms for the generation of productive contractile stress through different types of ring architecture.

FORCE GENERATION VIA THE CANONICAL MYOSIN-II MOTOR-DRIVEN MECHANISM

A common feature of the models described in this section is the exclusive focus on local contractility in a small, linearized segment of the ring without considering ring contraction as a global spatio-temporal macroscopic process. These models focus on specific properties of the myosin-II motors (e.g., force-velocity relation, assembly into thick filaments) and their interaction with actin filaments (e.g., sliding off the barbed end, filament buckling and bending). Largely assumed to operate as bipolar dimers (28), myosin-II motors activation produces a relative displacement of antiparallel actin filaments. Meanwhile, for a pair of parallel actin filaments, the motion of the myosin-II motor to their barbed ends does not generate filament sliding respectively to each other. However, these models did not account for the experimental observation that the amount of actin and myosin-II in the contractile ring decreases with time, possibly as a result of gradual shortening of actin filaments and removal of myosin-II motors from the ring. Furthermore, local actin filament deformation enhances the assembly of myosin-II molecules into bipolar filaments able to bind to multiple actin filaments, thereby effectively increasing the myosin-II duty ratio (29,30).

Carlsson (22) suggested a model of force generation in a gel-like structure that assumes isotropic three-dimensional orientation of actin filaments in a homogeneous actin gel with randomly distributed myosin-II thick filaments. The model finds that the maximal value of the contraction stress caused by both actin gel and myosin-II is proportional to actin filament length but experimentally determined parameters indicate it is up to an order of magnitude smaller than what is required for contraction. The experimental estimate is up to 10 nN for *D. discoideum* cells consistent with the estimate of the membrane tension of 1 nN/μm (31,32) and the ring perimeter of several microns. It was proposed that perhaps crosslinking of overlapping actin filaments increases the effective length of actin polymers, thus increasing the predicted maximal value for contraction stress (21,22).

The majority of contraction models assume that actin filaments are organized into a one-dimensional ring structure. The orientation of actin filaments and myosin-II distribution in such a structure might be either ordered or random. Contraction of an ordered 1D structure, as proposed for striated muscle or stress fibers, relies on the activity of myosin-II motors in a highly organized structure where the polarity of the actin filaments alternate periodically and active myosin-II is placed with constant spacing (33) (Fig. 1 *A*, *bottom*).

The ring, composed of one-dimensional organization of randomly oriented actin filaments, is probably the most structurally characterized to date (16). However, in such a structure, a pair of antiparallel filaments exist in both contracting (Fig. 1 *B*, *top*) and expanding (Fig. 1 *B*, *bottom*) configurations with approximately equal probability. In these two configurations, the rates of local contraction and expansion are equal, and therefore, no global contraction is expected. Thus, the question boils down to, how it is possible for this random filament structure to always generate contraction?

One possible answer is to determine if a random structure of actin filaments and myosin-II motors could evolve into a periodic sarcomere-like contractile structure. Zemel and Mogilner (28) and Craig et al. (34) considered dynamics of both actin filaments and myosin-II motors assuming that the motor slides off the barbed end of an actin filament as soon as it reaches the end. They showed that a homogeneous mixture of actin filaments with random polarity is unstable and spontaneously sorts into a set of clusters of filaments with opposite polarity. The reason for the instability is that in a cluster of filaments with a given preferential orientation, antiparallel filaments are moved fast by the motors into clusters of opposite directions, while the parallel filaments move much slower inside the cluster. The authors show that the action of myosin-II motors leads not to contraction, but to eventual expansion, of the actin filament structure.

In a different approach, Kruse and Jülicher (35) assumed that the motor reaching the barbed end of the actin filament does not slide off from the filament but, instead, lingers in this position. In such a position, the motor translocates the other filament as it continues to walk to its barbed end. The authors showed that alone, this assumption leads to contraction of the random filament structure as the sliding of parallel filaments always produce local contraction and subsequently breaks the symmetry between the contractile and expanding filament configurations.

The above models consider rigid actin filaments and assume that all myosin-II motors have identical dynamic properties when interacting with actin filaments. Recently, a novel mechanism explained the contractility in random filament structure caused by actin filaments buckling (36,37). The authors first considered a model of actin filaments and myosin-II motors with identical force-velocity relation (36). The net force exerted on each actin filament or motor is equal to zero assuming that the actin filaments motion is not affected by the drag force from the surrounding medium. It was demonstrated that in such a system, all motors are immobile while actin filaments move at velocities determined by their orientation and the distribution of the motors. As a result, the actin filaments eventually segregate according to their polarity and the contraction is

not observed. The authors conclude that myosin-II motor-based contractility requires existence of motors with nonidentical force-velocity relation to generate large enough forces to account for the elastic behavior of actin filaments (38).

Furthermore, the study showed that the symmetry between contractile and expanding behavior in the random filament structure can be broken due to asymmetric response of filaments to the different types of stresses, namely, a yielding tendency under compression and resisting extension (37). The underlying reason for this asymmetry is that the filament easily buckles under compressive stress created by motors of different velocities, with the buckling force for a filament segment of 1 μm in length to be ~1 pN (39). On the other hand, segments of the same actin filament under extensile stress do not change their size; and as a result, buckling of the compressed segments leads to the overall shortening of the filament (Fig. 2). Confirming this prediction in vitro, the authors observed that the number of buckles per filament rapidly increases during contraction and then decreases once the contraction ends. The model predicts that a high density of the motors prevents buckling due to strong crosslinking and smaller size of actin filament segments to be buckled. This prediction was supported by experimental estimates concerning the critical myosin-II concentration required for contraction within an order of magnitude. The authors also discussed a possible role of actin crosslinkers to increase the dispersion of the motor velocities and thus promote contraction. However, this projected effect may be inconsistent with the observation that a higher density of crosslinkers prevents buckling.

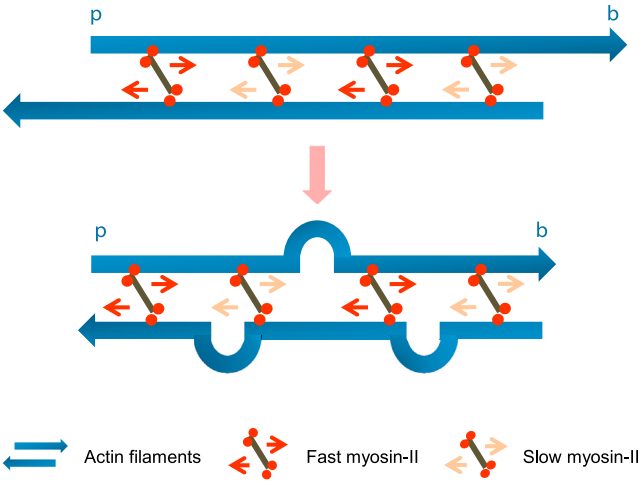

FIGURE 2 Different myosin-II velocities promote contraction due to actin filament buckling. The left-most myosin-II pulls the upper filament to the left faster than the neighboring myosin, thus promoting an extensile stress. At the same time, the lower filament is pulled to the right by the left-most myosin-II faster than by its neighboring motor, thus creating a compressive stress that leads to buckling (adapted from Figure 6 of Lenz et al. (36)). (*b*) Barbed and (*p*) pointed actin filament ends.

ACTIN DEPOLYMERIZATION-BASED MECHANISM OF FORCE GENERATION

A model of a global ring contraction introduces the notion of equal-sized contractile units, i.e., molecular structures made of actin filaments and myosin-IIs connected by delimiters: components whose number is in proportion to the number of the units, i.e., the initial ring size (40). The model assumes that all units shorten at the same rate, possibly as a result of actin depolymerization, since actin filaments shrink at a constant rate regardless of their length. As a result, the number of binding sites for myosin-II decreases at the same rate leaving the linear concentration of myosin-II motors constant. The dynamics of the delimiters differs from that of the actin and myosin-II: their number remains constant so that their concentration is predicted to increase as the ring contracts. This qualitative model explains the observed scaling of ring contraction speed (measured in units of length/time) to the initial ring size in *C. elegans* early embryos. The ring contraction requires attachment of the contractile units to the delimiters irrespective of whether the driving force comes from actomyosin filament sliding or actin depolymerization.

In addition to myosin-II, actin depolymerization was found to play a role in the dynamics of the contractile ring. Impairment of ADF/cofilin activity, actin depolymerizing proteins, leads to defective actomyosin ring contraction without perturbing its initial assembly in some model organisms (41–44). Studies in mammalian and *Drosophila* cells showed an aberrant accumulation of filamentous actin and myosin-II in the contractile ring in late cytokinesis in cofilin mutants (41,42,44), suggesting that ADF/cofilin proteins regulate actin and myosin-II turnover and disassembly during actomyosin ring contraction. Experimental data shows that actin depolymerization impacts ring contraction and that myosin-II motors, in addition to their classical role of filament sliding, promote actin depolymerization (45). In budding yeast, deletion of myosin-II motors or its regulatory light chain decreases the actin depolymerization rate by nearly 50%. Furthermore, genetic and chemical impairment of actin depolymerization, by ADF/cofilin loss of function mutation and Jasplakinolide treatment, respectively, decreases the rate of contraction by one-third when compared with WT budding yeast cells. A more drastic decrease in the contraction rate (from 60% to complete cytokinesis blockage) was observed when the previous treatments were respectively paired with the myosin-II motor deletion (45).

Zumdieck et al. (46) considered a model in which, in addition to the myosin-II motor-dependent stress generation, actin depolymerization directly produces sliding of actin filaments. This model involves actin filament depolymerization coupled with passive end-tracking crosslinkers to constitute a driving force for ring contraction. In the presence of the crosslinkers, actin depolymerization induces

relative motion between both antiparallel and parallel filaments, which breaks the symmetry between the contractile and expanding filament configurations. Zumdieck et al. (46) do not quantitatively consider microscopic kinematics of filaments' interaction with myosin-II motors and crosslinkers. The model considers only pairwise interactions between actin filaments and it is valid when the density of crosslinkers is low. This assumption may not hold in the contractile ring where a high density of active elements is likely to be required for generation of forces on the order of tens of nN. The myosin-II motor and actin depolymerization-based mechanisms are assumed to be independent.

A role for actin depolymerization in actomyosin ring contraction was further explored in a recent study (45). The model is essentially analogous to the Brownian ratchet for actin polymerization-driven membrane protrusion. When a cut in the actin filament occurs near a filament crosslinking site, thermal fluctuation of the crosslinker could allow its reattachment with the new filament end, leading to sliding of the filament caused by elastic energy stored in an elongated crosslinker (Fig. 3 *A*). When both motor-based and depolymerization-based contraction mechanisms are active, the model predicts that the ring always contracts independently of actin filaments organization. A qualitative explanation of this result is based on the following observation: For the motor-based mechanism the contraction rate for a pair of antiparallel filaments in a contractile configuration (Fig. 1 *B*, *top*) is equal to the rate of expansion in an expanding configuration (Fig. 1 *B*, *bottom*). The coexistence of motor-based mechanism and actin depolymerization-based mechanism guarantees an imbalance between contraction and expanding rates, resulting in the contraction of a one-dimensional ring with random filament alignment. In the contractile configuration, both motors and the actin depolymerization-based mechanism contribute (Fig. 3 *B*, *top*) to the contraction rate, whereas in the expanding configuration, only motors generate filament sliding (Fig. 3 *B*, *bottom*).

The above model could explain the observation that the actomyosin ring can contract, even in the absence of the motor, by relying on the coordinated action of actin depolymerization and crosslinking as the primary force for ring contraction. However, it does not provide any force estimates as it considers only kinematics of actin filaments. The processes of actin filament translocation by the myosin-II motor and the actin depolymerization-based mechanism are separated in time as the model simplistically assumes that the two mechanisms do not exert force on the same filament simultaneously. Nevertheless, model simulation of the experimental data suggests that there exists mutual influence between these two mechanisms as myosin-II motor activity seemed to increase the rate of actin depolymerization.

What major properties should the hypothetical crosslinker in this model have to produce ring contraction? Assuming that the relative contribution of motors and crosslinkers to force generation is invariant during contraction, the density of both entities may follow the same dynamics. The crosslinkers must also be mobile enough, as they spend only a fraction of time at the filament sliding-productive position near the filament pointed end, and they must not interfere with the myosin-II motor action.

A ROLE FOR MYOSIN-II MOTOR IN PROMOTING ACTIN TURNOVER

We have discussed two major mechanisms driving actomyosin ring contraction—one relying on myosin-II motor and the other on actin depolymerization joined with passive end-tracking crosslinkers. As of this writing, there are no known estimates of the relative contribution of each of these two mechanisms toward generation of the contractile force while

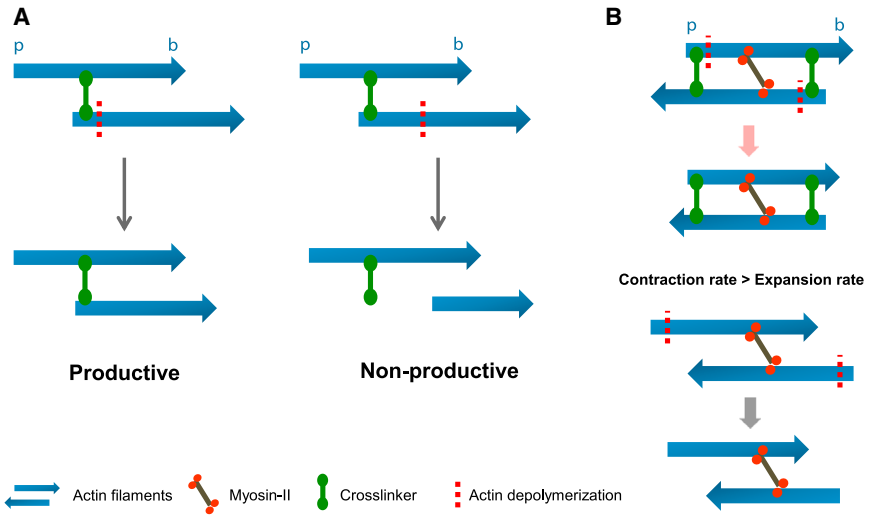

FIGURE 3 (*A*) Force generation due to actin depolymerization coupled with crosslinking (adapted from Figure 5A of Mendes Pinto et al. (45)). (*B*) Myosin-II motor sliding coupled with actin depolymerization in a contracting (*top*) and expanding (*bottom*) actin filaments configuration of an antiparallel actin filament structure. The two mechanisms generate a rate imbalance in favor of contraction. (*b*) Barbed and (*p*) pointed actin filament ends.

the estimates of the absolute value of force generated by myosin-II motors are in the range 4–15 nN (47–49). In some organisms, such as budding yeast, the myosin-II motors are dispensable for contraction (17–19), while in others (such as fission yeast) blocking the myosin-II motors activity leads to total cytokinesis failure (17). It is possible that there is crosstalk between the mechanisms, as several studies have suggested that myosin-II motors may play a role in actin depolymerization as well as motor-based contraction (15,50). Recent studies in both keratocyte actin structures and the budding yeast cytokinetic ring suggest that reduction in myosin-II motor activity results in significant decrease in actin depolymerization rate (45,51). Further, analysis of actin filament dynamics in vitro showed that myosin-II motors contract and disassemble antiparallel but not parallel actin filaments, suggesting that influence of myosin-II on actin turnover may depend on the geometry of actin filaments organization (52). We envision that using reconstituted, microscopy-based in vitro assays to examine the concerted actions of myosin-II and ADF/cofilin in modulating actin filament dynamics in the presence of different types of crosslinkers or stabilizers will lead to interesting insights.

How might myosin-II motor promote actin depolymerization? One possibility is that the sliding activity of myosin-II motor alters the conformation of actin filaments (53), and consequently affects the action of cofilin as a depolymerizing factor (54,55). Another possible explanation of this effect may be actin filament buckling, arising due to filament elasticity and disparity in myosin-II motors speed (37). It was demonstrated in vitro that bent actin filaments are prone to severing in the segments with high curvature (27). The authors of this article also suggest that the filament severing rate may increase due to adhesion of the filaments to the cell membrane, as crosslinking to the membrane effectively increases the compression stresses that promote filament buckling and bending. This results in an increase in the frequency of filament breaking due to myosin-II motor activity, and the consequent increase in the number of filament ends accessible for severing by cofilin molecules.

COMPLEMENTARY CONTRACTION MODELS

Until now, we have described the mechanisms built upon actomyosin ring structure and mechanics and its ability to generate force at the cleavage site. However, other auxiliary mechanisms may play an important role in actomyosin ring contraction; for example, changes in polar cortical tension, polar cortical cytoskeleton dynamics, cell adhesion, and turgor pressure (48). In different biological systems, these mechanisms likely contribute in different proportions to force generation.

It was recently presented that the polar actin cortex generates drag forces that resist contractile ring constriction and the release of polar stress induces furrow ingression (47,56). This observation suggests that in addition to ring mechanics, cortex mechanics also contributes to the overall process of contraction in cell division. The role of polar cortical stress can be explained through a viscoelastic model that underlies a possible mechanism for successful cytokinesis in adhesive and actomyosin ring deficient *D. discoideum* cells (19). This approach considers the cell as an elastic cylinder bridging two spherical daughter cells roughly describing the shape of a *D. discoideum* dividing cell (12,47). The cylindrical neck is under radial stress generated by cell adhesion to a substrate leading to the neck thinning. The resulting tension defines the Laplace pressure on the cell that depends on the local curvature. This pressure squeezes cytoplasm at the neck, and the cytosolic flow is resisted by the cortical polar tension of the daughter cells. As a result, the bridge thinning dynamics is determined by the difference (~0.025 nN/μm^2) between the radial stress (~0.04–0.1 nN/μm^2) applied to the cylinder surface and the compressive stress from the daughter cells. Release of the polar cortical tension plays an important role in the initial furrow ingression in mammalian cells, and it was shown that increase of the polar tension may lead to the cytokinetic shape oscillatory instability (56).

In contrast to mammalian cells, in walled cells where polar cortex dynamics seems to have a negligible role in furrow ingression, high turgor pressure has been shown to strongly influence the cleavage rate. A recent study, performed in *S. pombe* cells, showed that a ratchet-like mechanism of septum fibril polymerization provides a pushing force (1 nN/μm^2) into the cytoplasm of the same order of magnitude as the turgor pressure to allow septum ingression (57). Based on the number of myosin-II molecules in the cell, an estimate of the maximal force due to actomyosin ring is ~10–15 nN with the equivalent stress of 10 pN/μm^2, thus giving the contribution of the ring ~1% of the total force required for cytokinesis.

SUMMARY

An emerging view in contractile ring mechanics reveals a dual role for myosin-II in actin filament sliding and actin filament depolymerization. Both roles are in turn affected by the structural organization of actin filaments. A ring with random actin filament orientation incorporates expanding and contractile configurations but its ability to drive cleavage furrow ingression lies in an inherent asymmetry that favors the contractile configuration. It remains to be seen to what extent myosin-II and actin depolymerization-based mechanisms contribute to contractile ring dynamics, how they are coupled with the overall cell mechanics in different model organisms, and whether both mechanisms are always coupled in cellular processes involving actomyosin-based contractility.

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