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Membrane Bending by Actin Polymerization

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Abstract

Actin polymerization provides driving force to aid several types of processes that involve pulling the plasma membrane into the cell, including phagocytosis, cellular entry of large viruses, and endocytosis. In endocytosis, actin polymerization is especially important under conditions of high membrane tension or high turgor pressure. Recent modeling efforts have shown how actin polymerization can give rise to a distribution of forces around the endocytic site, and explored how these forces affect the shape dynamics; experiments have revealed the structure of the endocytic machinery in increasing detail, and demonstrated key feedback interactions between actin assembly and membrane curvature. Here we provide a perspective on these findings and suggest avenues for future research.

Introduction

Bending of internal and external membranes is essential for many cellular processes, including the formation of protrusions that explore the environment or drive cell migration, cytokinesis, internalization of molecules and organisms from outside the cell, and membrane trafficking. Forces that bend the membrane include those from curvature-generating proteins (CGPs) that form a layer on the membrane, asymmetries between membrane leaflets, osmotic pressure, myosin activity, and actin polymerization. Actin-based forces are crucial for protrusion and cytokinesis, and they have been studied in detail via both experiments and modeling analysis (1, 2). Actin polymerization is also important for generating pulling forces to drive several types of engulfment processes, usually working in concert with CGPs. Actin is usually required when the force barrier is large, the engulfed object is large, or key proteins are missing. Endocytosis in mammalian cells requires actin under conditions that include tight substrate attachment (3) and increased membrane tension (4, 5). Clathrin-mediated endocytosis in yeast requires actin (6). In phagocytosis, actin polymerization creates protrusions around the target (7), and is required for bead internalization (8). Cellular entry of large virus particles, either spherical or elongated, requires actin polymerization (9–11). Entry of apicomplexan parasites also requires actin in the host cell (12). Finally, actin polymerization is important in vesicle trafficking (13, 14).

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Here I review recent work treating the biophysical mechanisms by which actin polymerization aids endocytosis. To give an up-to-date account, I focus on papers published in the last two years; Refs. (15, 16) give more comprehensive reviews. There has been progress in understanding i) the general mechanisms of pulling force generation by inhomogeneous actin polymerization, ii) how a spatial distribution of actin polymerization, in conjunction with CGPs, controls the shape of an invagination over time, iii) how feedback between force and chemistry modulate protein dynamics, and iv) the types of additional mechanisms that assist actin polymerization in overcoming large force barriers or reduce these barriers.

General mechanism of pulling force generation by actin polymerization

A concise relationship between the spatial distribution of actin polymerization and the membrane forces gives useful perspective on the bending mechanisms. A focus of polymerization generates a center of pushing force surrounded by pulling forces, while a local polymerization “hole” generates a center of pulling force surrounded by pushing forces (see Fig 1). Actin polymerization surrounding the hole drives retrograde flow, which pulls the actin in the hole region backwards into the cell, creating the pulling force. Ref. (17) developed a quantitative relationship between polymerization and force, treating the actin network as an elastic medium with stiffness (Young’s modulus) E , bounded at the $x - y$ plane by a rigid membrane. Inhomogeneous actin polymerization was described by $g(x, y)$, the total extent of z -direction growth. For growth varying in the x -direction with wavelength L , $g(x, y) = g_0[1 + \cos(2\pi x/L)]$, the actin force density $f_a(x, y)$ was

$$f_a(x, y) = \frac{2\pi g_0 E}{3L} \cos(2\pi x/L). \quad (1)$$

For uniform polymerization ($L \rightarrow \infty$), $f_a = 0$ because the actin network treadmills into the cell; unless it is attached to an internal organelle or to a substrate, this requires only enough force to overcome the viscous drag force, which is much smaller than membrane-bending forces. Thus forces are generated by **differences** in actin polymerization from point to point. Since $f_a(x, y)$ is proportional to E , effective force generation requires a stiff actin network. Strong membrane attachments are also required in regions of pulling force.

Dynamic control of membrane by actin polymerization forces

Refs. (18–21) have examined how actin and CGPs jointly determine the membrane shape, using assumed spatial distributions of the actin-polymerization force. Equilibrium membrane configurations for z -direction actin forces were calculated by minimizing a continuum model of the free energy W :

$$W = \int_S [2\kappa(C - C_0)^2 + \sigma] dS + P_0 V - \int_S f_a z dS \quad (2)$$

Here S is membrane area, κ is the bending stiffness, C is the local curvature, C_0 is the preferred curvature imposed by CGPs, σ is the membrane tension, P_0 is the turgor pressure, f_a is the assumed actin force density, z is the displacement of the membrane, and V is the volume of the invagination. The first three terms describe energy penalties for curvature different from the preferred value, pulling membrane area into the invagination, and creating volume against the osmotic pressure, while the last term describes the energy from actin polymerization. Additional terms were used to describe actin forces in other directions and other contributions to the curvature energy.

Several types of actin force distributions were treated. Refs. (20) and (21) treated pulling forces spread out over on a disk of radius 30–50 nm, balanced by an outer ring-shaped distribution of pushing force from actin polymerization (see Fig. 2A), as was proposed in Ref. (22). Ref. (18) treated a central point pulling force (Fig. 2B). Ref. (19) treated a ring-shaped distribution of pulling forces. Refs. (19–21) also treated lateral forces (Fig. 2C), as suggested by Ref. (23).

For low or vanishing turgor pressure, the actin force made the difference between arrested invagination and complete budding (19–21). The details differ from model to model. Ref. (20) found a “snap-through instability” as a function of actin force at a membrane tension of 0.08 mN/m, in which a tube shape suddenly transforms to a vesicle attached by a long tether. The pushing force required to invaginate the membrane was 190 pN in an “actin-only” model, and about 30% less when CGPs were included. Since a polymerizing actin filament can probably generate a force of a few pN, these forces correspond to 50–100 growing filaments. On the other hand, Ref. (21) found that at a lower membrane tension of 0.02 mN/m, with coat proteins having the same stiffness as the membrane, actin polymerization eliminates a snap-through instability as a function of coat-protein area (Fig. 3A). A similar effect occurred in calculations with a higher coat-protein stiffness, at a higher membrane tension of 0.2 mN/m. The actin forces required to overcome the lower membrane tension were less than 15 pN. Ref. (19) predicted that a “pearling instability” could assist vesicle pinch-off.

Ref. (18) used a higher turgor pressure value of 1 MPa to treat yeast, using the balance of forces shown in Fig. 3B. The turgor pressure dominated the force opposing invagination, and an actin force of about 3000 pN was required to form a vesicle. This force is larger than can be generated by the 100–150 growing filaments (24) at the endocytic site. The actin force led to neck constriction in the presence of spontaneous curvature from CGPs. Anisotropic CGPs were also found to stabilize the invagination.

The disk/ring force distribution (Fig. 2A) assumed in Refs. (20) and (21) is supported by a recent estimate of the actin force from measured membrane-deformation profiles (17). A force balance on the membrane was set up including contributions from membrane bending, membrane tension, turgor pressure, cell wall, and actin polymerization. The first four contributions were obtained from the measured profiles and a calculation of the cell-wall force. This allowed the actin-polymerization force density to be obtained. The pulling force distribution was spread out over a central disk of radius about 40 nm. It was balanced by a larger region of pushing forces,.

The spatial distribution of actin polymerization required to generate this force profile was obtained using an elastic-gel model of a growing actin network (17). A ring-shaped distribution of actin growth, surrounding a disk of “passive” actin attached to the membrane, produced the required force distribution. This mechanism places stringent requirements on the actin gel, requiring a Young’s modulus ~ 80 kPa, and growth forces >10 pN per filament.

The general mechanism assumed in several of these models, is supported by recent correlative light and electron-microscopy experiments, in which the membrane-binding regions of Sla2 (yeast homolog of Hip1R), which links actin to the membrane, or the entire crosslinking protein Sac6 (yeast fimbrin), were deleted (25). In Sla2-mutated cells, actin patches formed at the membrane, but no bending was observed, consistent with Sla2 acting to transmit pulling forces from the actin network to the membrane. Deletion of the crosslinker Sac6 prevented or reduced membrane bending, consistent with the requirement of a stiff actin gel for successful endocytosis. A ring-shaped region of actin polymerization is also consistent with recent experiments (J. Ries, personal communication, 2016) showing that a ring of the actin nucleation promoting factor (NPF) Las17 surrounds a Sla2 disk.

Mechanochemical feedback loops and their effect on protein dynamics

A stochastic 3D model of the actin network (24) treated protein dynamics and membrane deformation simultaneously, building on previous work (26). The network was grown explicitly in three dimensions from a preexisting ring of the actin NPF Las17 and taken to be infinitely rigid. A negative-feedback interaction was assumed, in which filament branching events can detach and inactivate a Las17 molecule from the membrane with finite probability. Pulling forces were assumed to turn on at a certain critical number of filaments and subunits. As in Ref. (18) it was found that actin polymerization was too weak to overcome commonly accepted turgor pressure forces. A smaller value was used, on the assumption that other factors provide the remaining force, or reduce the force requirements. This model reproduced the pulse behavior of NPFs and F-actin during CME in yeast, and explained the effects of several other mutations (24). It also predicted an increase in Las17 count upon reduction of Las17 branching activity, which was confirmed by measurements of the Las17 count.

Recent work placing cells on curvature-inducing nanopillars has clarified mechanochemical interactions in endocytosis (27). Proteins preferentially recruited to curved membrane regions included actin, the actin NPF cortactin, and the curvature-generating proteins clathrin and epsin. Because actin polymerization generates membrane curvature, these findings imply that actin and membrane curvature constitute a positive-feedback loop. There are also negative-feedback loops connecting actin polymerization with membrane bending. For example, the curvature-generating protein FBP17 assists actin polymerization, but actin polymerization creates membrane tension that inhibits FBP17 assembly (28).

Factors that could increase actin polymerization forces or reduce the required force barrier in yeast

The above calculations suggest that it is difficult for polymerizing actin filaments to overcome generally accepted turgor pressure values of 0.5 MPa or more in yeast. The following factors could either increase the force available, or reduce the force requirements.

Lateral polymerization

The actin force estimates assume a branched network of actin filaments, as suggested by Ref. (29), at fixed orientations. However, the orientation of the filament tips during endocytosis is not known. The amount of force that can be generated by a filament increases if it is oriented nearly parallel to the membrane (30). Ref. (31) showed that filaments polymerizing laterally into a wedge-shaped space between the membrane and the rest of the actin network could generate very large forces. This model is consistent with the finding (32) that newly polymerized actin is incorporated near the membrane, but does not explain why Arp2/3 complex assembles farther from the membrane than actin (32). On the other hand, forces from the membrane onto filament tips will also bend them toward the plane of the membrane, increasing their force-generating potential.

Motor activity

Inward motion of the membrane during endocytosis in yeast requires Type-I myosin motor activity (33), which could enhance the actin force in at least two ways. First, myosins could move along actin scaffolds while bound to the membrane, thus pulling the membrane out if the scaffold is oriented appropriately (34–36). Recent work has measured forces associated with membrane-bound Type-I myosins (37). Forces of about 1 pN could be generated parallel to a lipid bilayer (Fig. 4A); they were limited by myosin diffusion in the bilayer. Such frictional forces can enhance vesicle scission (36). Larger forces might be obtained in cells because membrane proteins could increase the myosin friction. Lateral forces can be converted to pulling forces by a “zippering effect” (Fig. 4B), which also amplifies the force. Second, myosins simultaneously attached to the membrane and an actin filament barbed end, if appropriately oriented, could push the growing filament far enough away from the membrane to allow barbed end polymerization even against a large opposing force.

Channel localization

Turgor pressure in yeast is regulated by channel proteins that control osmolyte outflow. Therefore a channel cluster might reduce the turgor pressure locally. The yeast glycerol channel Fps1 accumulates in patches (38). In addition, the Kv3.3 channel (in CHO cells) is associated with actin polymerization (39), and a similar association of channels with endocytic actin patches might occur in yeast. The effects of channel clusters at endocytic sites was explored by calculations of the osmolyte concentration profile around a membrane patch with increased permeability (40). The turgor pressure was reduced by a fraction determined by the ratio pa/D , where p is the enhanced permeability, a is the radius of the leaky region, and D is the osmolyte diffusion coefficient. A cluster of 60 channels locally reduced the turgor pressure by 50%, greatly reducing the force requirements for endocytosis.

Smaller turgor pressure than is generally assumed

Measured turgor pressure values are highly uncertain. The turgor pressure is often measured by increasing the external osmolyte concentration and evaluating at what point the cell membrane experiences zero net osmotic force. Since osmoregulation will increase the internal osmolyte concentration, this method may overestimate the turgor pressure. A recent rapid indentation method (41) overcame this limitation. This led to a turgor pressure of 0.2 MPa for budding yeast, considerably smaller than most measured values. However, purely mechanical measurements of the turgor pressure in fission yeast (42) have yielded values of over 1 MPa, and it is not clear how osmoregulation would affect these measurements.

Conclusion

Work over the past two to three years has solidified a general picture of the effects of actin polymerization on membrane bending during endocytosis. Actin pulling forces, in addition to overcoming mechanical barriers, can have characteristic effects on the dynamic shape of a forming vesicle. The forces can be generated by a preexisting chemical pattern of actin NPFs and attachment proteins. Actin also participates in feedback loops controlling protein dynamics. However, numerous questions remain unanswered. For example, it is not known how the chemical pattern is formed in the membrane, and how its size is established. Possible mechanisms include a two-dimensional chemical instability, and a mechanically limited growth process analogous to that limiting the size of actin bundles (43). The orientation of the growing actin filament tips, which determines their force-generating capability, is not known. The geometric arrangement of Type-I myosins and actin filaments that generates pulling force has not been established. The biophysical mechanisms underlying the negative-feedback interaction between actin and the NPFs remain to be pinned down. Finally, the extent to which channels affect the turgor pressure at the endocytic site is unknown.

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Figure 1.

Membrane bending by inhomogeneous actin polymerization. Red denotes extent of polymerization near the membrane (green). A focus of polymerization leads to localized pushing force balanced by a ring of pulling force; a local slowing of polymerization leads to localized pulling force balanced by a ring of pushing force.

Figure 2.

Assumed distributions of forces used to calculate effect of actin polymerization on vesicle budding. A) Balancing, distributed vertical forces. B) Single pulling force at middle of invagination. C) Lateral forces.

Figure 3.

Simulation results. A) Zero turgor pressure. Small actin force drives transition from “U”-shaped to “Ω”-shaped bud at an intermediate membrane tension. Taken from Ref. (21). B) Force balance during endocytosis in cells with high turgor pressure. The turgor pressure Π pushes up on the membrane, while actin-polymerization forces and forces from the cell wall pull down. Modified from Ref. (18) by inverting. C) Stochastically modeled actin network structure for a Sla2-null cell. There is no membrane bending, consistent with Ref. (25), but actin forms a comet tail. Taken from Ref. (24).

Figure 4. Lateral force generation by Type-I myosin. A) 150 myosins in lipid bilayer on bead. Lower panel is covariance trace of beads used to hold actin filament. Inset is expanded view of first 15 seconds. B) Leftward motion of myosins creates pulling forces on membrane. Modified from Ref. (37).