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Membrane bending by actin polymerization

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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.

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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].

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: firstly, the general mechanisms of pulling force generation by inhomogeneous actin polymerization; secondly, how a spatial distribution of actin polymerization, in conjunction with CGPs, controls the shape of an invagination over time; thirdly, how feedback between force and chemistry modulates protein dynamics; and finally, the types of additional mechanisms that assist actin polymerization in overcoming large force barriers or reduce these barriers.

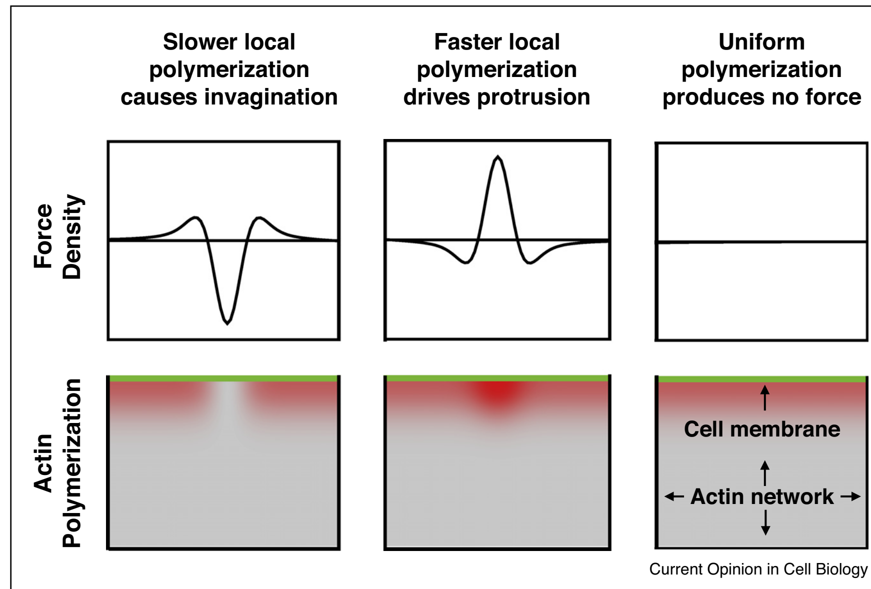
General mechanism of pulling force generation by actin polymerization

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 Figure 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

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

For uniform polymerization ($L \to \infty$), $f_a = 0$ because the actin network treadmills into the cell; unless it is attached

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.

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•,19,20,21•] 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:

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

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. [20,21•] 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 Figure 2a), as was proposed in Ref. [22]. Ref. [18•] treated a central point pulling force (Figure 2b). Ref. [19] treated a ring-shaped distribution of pulling forces. Refs. [19,20,21•] also treated lateral forces (Figure 2c), as suggested by Ref. [23].

For low or vanishing turgor pressure, the actin force made the difference between arrested invagination and complete budding [19,20,21•]. 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

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