Actin takes its hat off to dynamin

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A major player in membrane traffic, the large GTPase dynamin, is known in the actin dynamics field for its indirect association with the actin cytoskeleton via actin-binding proteins (ABPs) like cortactin. In this issue of *The EMBO Journal*, Gu *et al* extend this picture by revealing a direct interaction between dynamin and F-actin. They further show that oligomerized dynamin kicks off the gelsolin cap at the barbed ends of filaments. This study not only provides an interesting link between actin remodelling and membrane dynamics via dynamin, but also sheds light on the long-standing mystery of how barbed ends are liberated from the high-affinity capping protein gelsolin.

For most people, dynamin belongs to the cell membrane dynamics world, and is particularly recognized for its role in endocytosis where it combines membrane deformation and fission activities (Praefcke and McMahon, 2004). Recent work has fleshed out a molecular model for dynamin function, whereby the dynamin helix undergoes a unique mechanical sequence of constriction and torsion followed

by depolymerization in order to break membranes (Lenz *et al*, 2009). While it is clear that dynamin is also involved in actin dynamics, only indirect interactions with filamentous actin have been reported in which the proline-rich domain (PRD) of dynamin interacts with the SH3 domains of ABPs such as cortactin (Orth and McNiven, 2003; Mooren *et al*, 2009). In this scenario, it is unclear how the nucleotide load of dynamin could influence actin dynamics and how actin dynamics could interfere with the GTPase activity of dynamin. Surprisingly late in the long history of dynamin–actin interaction, and thus even more remarkably, Gu *et al* show not only a direct interaction between these two major players of intracellular dynamics, but also that the dynamics of actin and dynamin are coupled.

First, Gu *et al* identify an F-actin-binding site in dynamin and show that binding is increased or decreased in predictable ways by mutating specific charged residues. WT dynamin expressed *in vitro* or a mutant lacking its PRD domain are both active for actin filament binding, providing further evidence that this interaction is direct and not mediated by

Figure 1 Dynamin binds F-actin, but only oligomerizes on short actin filaments. Filaments capped with gelsolin have a modified conformation (bright red filaments), which perhaps reverts to normal (faint red filaments) upon dynamin binding and oligomerization. This expels the gelsolin and permits barbed end elongation. Once the filament is over ~700 nm in length, dynamin disassembly leads to the re-binding of gelsolin.

other ABPs. Compared with other ABPs, dynamin has an acceptable affinity (sub μ M Kd), but exhibits lower actin bundling activity than α -actinin. However, dynamin's bundling activity is enhanced in the presence of lipids, suggesting an interesting on-off switch for bundling at membranes. However, given this direct interaction with filamentous actin, it is somewhat surprising that Gu *et al* do not observe a more marked colocalization with stress fibres in their *in vivo* studies. The association of dynamin with the actin of focal adhesions is much more convincing, but with the caveat that focal adhesions could be enriched in dynamin because of the high density of the clathrin machinery at these sites (Maupin and Pollard, 1983).

In the second part of the paper, the authors seek a link between dynamin's actin-binding capacity and dynamin's mechanochemical properties of oligomerization and concomitant nucleotide hydrolysis. Short actin filaments, created by gelsolin or by shearing, accelerate dynamin's GTPase activity (and oligomerization), while G-actin and long filaments have no effect. This again implies a possible on-off switch at membranes where nascent filaments formed by membrane-recruited nucleation promoting factors are generally short. Importantly, mutants that do not bind F-actin do not accelerate GTP hydrolysis of dynamin even in the presence of the short filaments. Why short actin filaments stimulate oligomerization and GTPase activity of dynamin, while longer ones do not, remains a mystery, but one could imagine that this might be due to orientation or steric effects, which would be more pronounced for an entangled network of long filaments.

The ultimate question of the paper is what dynamin oligomerization means for actin dynamics. The authors show that oligomerized dynamin has no effect on F-actin formation on its own, and that it also does not reverse the inhibitory effect of heterodimeric capping protein (CP) on actin polymerization. In contrast, gelsolin-capped filaments are observed to grow under conditions in which dynamin oligomerizes, indicating that the dynamin oligomer is somehow removing the gelsolin hat from the barbed end. Liberation of free barbed ends is dependent on dynamin's F-actin-binding capacity, and the authors further show that oligomeric dynamin displaces

gelsolin from actin filaments, although dynamin does not bind the barbed end. Gelsolin and CP have a high affinity (nM Kd) for F-actin, predicting a long half-life for a capped barbed end, which is incompatible with fast actin remodeling in the cell (Zigmond, 2004). This inconsistency has led to the search for factors capable of removing capping proteins from barbed ends, but no such 'uncapping' protein has yet been identified for gelsolin, although Ena/VASP proteins are known to delay gelsolin binding in what is known as an 'anticapping' strategy (reviewed in Trichet *et al*, 2008). Putting everything together (Figure 1), oligomeric dynamin, created by interaction with short actin filaments, has the function of an 'uncapper', thus contributing to filament elongation and actin dynamics. The mechanism by which dynamin removes gelsolin from barbed ends remains an open question. Gelsolin is believed to impose a conformational change on the actin filament (Allen and Janmey, 1994; McGough *et al*, 2003). One possibility is that oligomeric dynamin restores the normal twist of the actin filament, thus disrupting the interaction of gelsolin with the barbed end.

With this study by Gu *et al* (2010), dynamin enters the ranks as a *bona fide* ABP and rises to fame as the first known actin filament uncapping protein effective against gelsolin. However, even though this study solves an essential question of actin dynamics, it leaves a fundamental question in the field of dynamin unanswered: where and why actin is needed for membrane traffic. It is known that actin is absolutely required for dynamin-mediated membrane fission (Doherty and McMahon, 2008), but the picture drawn here of the dynamin-actin interaction looks much more dynamic than assumed initially. If the interactions of dynamin with nucleation promoting factors and other ABPs are summed up with gelsolin removal activity, actin growth and turn over at dynamin sites must be quite intense. This reinforces the idea that dynamic forces exerted by actin are crucial for dynamin's fission activity.

Conflict of interest

The authors declare that they have no conflict of interest.

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