Proteins That Regulate Dynamic Actin Remodeling in Response to Membrane Signaling Minireview Series*

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The actin cytoskeleton is a dynamic structure that responds to multiple extracellular stimuli. It contributes to cell-cell and cell-substrate interactions by providing a structural framework and by modulating signal transduction cascades. It also generates movements to carry out many fundamental cell processes, such as lamellipodial and growth cone extension, chemotaxis, endocytosis, exocytosis, and cytokinesis. Proteins that regulate the assembly and disassembly of the actin cytoskeleton in response to signaling are therefore studied with intense interest. This series focuses on several key players that are modulated by the rho family of small GTPases and by phosphatidylinositol 4,5-bisphosphate (PIP2)1 (Table I). Rac, Rho, and Cdc42 GTPases control the organization of the actin cytoskeleton (reviewed in Ref. 1) and may also regulate the synthesis of PIP2 by associating with phosphatidylinositol 5-kinases (reviewed in Ref. 2). PIP2 has a pivotal role in the phosphoinositide cycle and can serve as a spatially localized membrane signal that recruits and modulates proteins required for signal transduction, cytoskeletal regulation, and membrane trafficking (reviewed in Refs. 2 and 3).

Following receptor activation, actin scaffolds are disassembled in some parts of the cells, while new scaffolds are built elsewhere. Actin polymerization at the plasma membrane and at membrane vesicles can generate protrusive force that does not depend on actomyosin interactions. Actin filaments grow by adding monomers to the barbed (plus or fast polymerizing) end of an actin-nucleating site near the membrane and depolymerize deeper within the cytoplasm (4). Control of actin dynamics is a complex process that is regulated by many proteins. Because of space limitations, only four groups of proteins are reviewed here (Table I). These proteins have been implicated by studies using intact cells, permeable cells, cell-free extracts, and reconstituted proteins. Much insight has also been obtained by using intracellular pathogens such as Listeria monocytogenes to dissect the requirements for actin-based motility downstream of signaling.

Actin nucleation is the rate-limiting step in polymerization, and barbed end nucleating sites are generated as follows (Fig. 1). First, they are generated by de novo nucleation. Actin nucleation requires actin association into trimers. The actin-related protein Arp2/3 complex, which caps the pointed end of actin, initiates polymerization in the barbed direction. Proteins in the Wiskott-Aldrich syndrome protein family (WASP) stimulate nucleation by Arp2/3, and the small GTPase, Cdc42, and PIP2 increase the activity of some of the WASp family proteins. Henry N. Higgs and Thomas D. Pollard will review WASp family proteins. Masaya Yamamoto, Marisan Mejillano, and Helen L. Yin will review this subject in the last article of this series. Second, barbed end nucleating sites are generated by severing preexisting actin filaments to create barbed ends. Gelsolin is a premier example of a severing protein. Micromolar Ca2+ activates gelsolin. Because gelsolin caps the barbed end of actin filaments after severing, it has to be subsequently dissociated to create free barbed ends for rapid barbed end elongation. PIP2 and Rac promote gelsolin uncapping. Actin-depolymerizing factor (ADF) and a related protein, coflin (referred to collectively as ADF/cofilin), promote filament breakage and do not cap filament ends after breakage. They also contribute to actin dynamics in other important ways (see below). Therefore, gelsolin and gelsolin-like proteins are likely to be the major severing proteins in cells. Hui Qiao Sun, Masaya Yamamoto, Marisan Mejillano, and Helen L. Yin will review this topic in the second article of this series. Third, barbed end nucleating sites are generated by uncapping preexisting filaments without severing. Proteins that cap barbed ends without severing include a gelsolin relative, CapG, and the unrelated capping protein. They are also important for the termination of filament polymerization. The three mechanisms for promoting nucleated actin assembly are not mutually exclusive. Cells may use different combinations, in response to different messengers, to generate an expanded repertoire of cytoskeletal responses.

Rapid actin polymerization at the leading edge must be balanced by depolymerization elsewhere to maintain the supply of actin monomers for addition to the growing filaments. ADF/cofilin promotes actin filament depolymerization by severing and by increasing subunit dissociation. ADF/cofilin is inhibited by phosphorylation and by PIP2. Lim kinase, a Rac effector, phosphorylates ADF/cofilin. Marie-France Carlier, Fariza Ressad, and Dominique Pantaloni will review this topic in the third article of the series.

Polymerized actin filaments are frequently attached to the plasma membrane to form a cortical scaffold. Ezrin, radixin, and moesin are closely related cross-linking proteins that attach actin filaments to several integral membrane proteins. They are referred to collectively as ERM, and they have an important role in the organization of the cortical actin network and mediating membrane/cytoskeletal cross-talk. ERM is activated by PIP2 through a Rho-dependent pathway, and the active ERM conformation is maintained by phosphorylation. Sachiko Tsukita and Shigenobu Yonemura will review this subject in the last article of this series.

The emerging relation between receptor signaling, phosphoinositides, small GTPases, and actin dynamics, together with the discovery of new actin regulatory proteins and confirmation of the importance of previously identified proteins, has been very exciting indeed. The major thrust in the future is to determine how these proteins contribute to cytoskeletal remodeling in a spatially and temporally defined fashion. Much progress has been made recently (5, 6), and we may soon be able to propose an integrated model for the complex intersecting pathways between signaling and actin dynamics.

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1 The abbreviations used are: PIP2, phosphatidylinositol 4,5-bisphosphate; ADF, actin-depolymerizing factor.
**Table I**

*Summary of actin regulatory proteins reviewed in this series*

PIP2 and phosphorylation in the WASp-Arp2/3 column refers to N-WASP. The primary small GTPase that is functionally linked to each protein is listed; in some cases, additional GTPases have been implicated. The effect of phosphorylation on protein activity is indicated in parentheses. Upward arrow, activates; downward arrow, inactivates; ND, not determined.

| Protein     | Effects on actin                                                                 | Regulation | Small GTPase |
|-------------|---------------------------------------------------------------------------------|------------|--------------|
| WASp-Arp2/3 | Pointed end capping; de novo nucleation; cross-links F-actin into Y branch network | ↑, No, Yes (ND), ND | Cdc42        |
| Gelsolin    | Strong, stoichiometric severing; barbed end capping/uncapping                   | ↓, ↑, Yes (ND), ↓ | Rac          |
| ADF/cofilin | Changes twist of F-actin; increases pointed end off rate; weak, nonstoichiometric severing | ↓, No, Yes (↓), ↑ | Rac          |
| ERM         | Attaches F-actin to membrane receptors                                           | ↑, No, Yes (↑), ND | Rho          |

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