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Roles of ADF/cofilin in actin polymerization and beyond

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Abstract

In collaboration or competition with many other actin-binding proteins, the actin-depolymerizing factor/cofilins integrate transmembrane signals to coordinate the spatial and temporal organization of actin filament assembly/disassembly (dynamics). In addition, newly discovered effects of these proteins in lipid metabolism, gene regulation, and apoptosis suggest that their roles go well beyond regulating the cytoskeleton.

Introduction and context

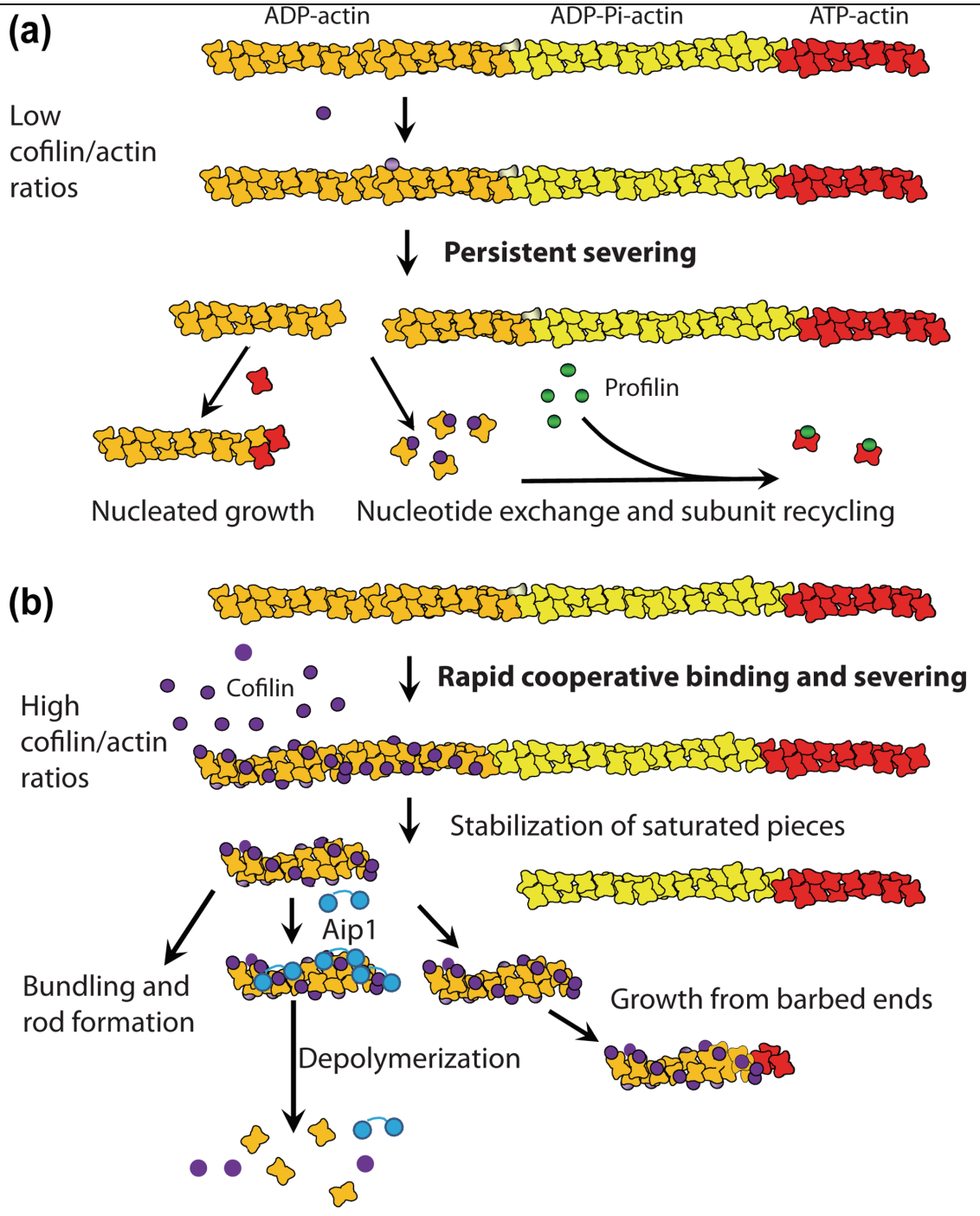
All eukaryotes express at least one member of the essential actin-depolymerizing factor (ADF)/cofilin family of actin-binding proteins [1]. Three forms are expressed in mammals: ADF (also known as destrin); cofilin-1, the major ubiquitous form in non-muscle tissue; and cofilin-2, the major form in differentiated muscle. *In vitro*, ADF and cofilin-1 are qualitatively similar in many of their actin-dynamizing activities and regulation but differ quantitatively. ADF has a weaker nucleating ability than cofilin and thus can serve as a monomer-sequestering protein for ATP-actin at concentrations in which cofilin would enhance assembly of the cofilin-ATP-actin complex [2,3]. However, at the physiological molar ratios to actin (generally 1:25 to 1:4), both ADF and cofilin bind ADP subunits in filamentous actin (F-actin) and sever filaments, leading to enhanced actin dynamics [2]. Silencing and rescue experiments of ADF and cofilin in cultured cells show that either protein can rescue defects in cytokinesis and cell motility [4], although there are suggestions in the literature that the two proteins differ in their ability to regulate cell migration in three-dimensional matrices, with ADF being the more important protein for cell invasion through Matrigel [5]. Knockout of the cofilin-1 gene in mice is embryonic lethal [6], whereas the only gross deficit in ADF knockout mice is postnatal blindness due to corneal thickening at about 4 weeks [7]. Because cofilin-1, the most ubiquitous of the isoforms, is usually expressed at higher levels and has been studied more intensely because of its essential role in development, this review will focus on cofilin-1, hereafter just called cofilin.

Major recent advances

Mechanism and function in actin dynamics

Cofilin is best known as a regulator of actin filament non-equilibrium assembly/disassembly. Whether cofilin promotes actin assembly or disassembly depends upon the concentration of cofilin relative to actin and the relative concentrations of other actin-binding proteins [1,8]. *In vitro* studies have demonstrated that if the ratio of cofilin/actin subunits in a filament is low (less than 1%), this results in persistent filament severing (Figure 1) [8]. At higher cofilin/actin molar ratios (1:10 to 1:2), cofilin severs rapidly but transiently because it binds F-actin cooperatively and stabilizes F-actin in a twisted form as it saturates the severed pieces. Indeed, the assembly of the cofilin-ADP-actin complex into non-dynamic actin bundles (also called rods) is an important energy-conserving mechanism that in most cells is readily reversible (Figure 1); however, in axons and dendrites of stressed neurons, the rods block transport and cause loss of synapses [9], perhaps contributing to dementias, including Alzheimer disease [10].

Figure 1. Concentration-dependent effects of cofilin on actin dynamics



(a) Cofilin (purple) binds preferentially to ADP-actin (orange) and, at low stoichiometry with respect to actin subunits, severs filaments, creating new barbed and pointed ends. The cofilin dissociates with an actin subunit in the ADP form, and nucleotide exchange, enhanced by Srv2/CAP1 (exchange factor for actin-bound nucleotide when complexed to cofilin) and/or profilin (green), occurs on the actin. Cofilin can recycle to sever again. The pieces of filamentous actin (F-actin) generated can nucleate filament growth or can enhance depolymerization if assembly-competent ATP-actin is limiting. **(b)** At higher stoichiometry, cofilin binds to ADP-actin, but since binding is cooperative, regions of the F-actin become saturated and stabilized in the 'twisted form'. Severing occurs rapidly, but as the cofilin is sequestered on the pieces of actin, severing is not persistent. Fragments are further depolymerized in the presence of actin-interacting protein 1 (Aip1) (blue) to generate monomer or can be used to nucleate growth. In cells under stress where ADP-actin levels are elevated, the cofilin-saturated F-actin assembles into rod-shaped bundles.

Other actin-binding proteins may enhance, modulate, or eliminate cofilin effects on actin dynamics. Among the best studied of these are actin-interacting protein 1 (Aip1) (also known as WDR1), tropomyosins, cortactin, actin-related protein 2 and 3 (Arp2/3) complex, coronins, and Srv2/CAP1 (exchange factor for actin-bound nucleotide when complexed to cofilin). Aip1 binds to cofilin-actin filaments and enhances the severing and depolymerizing activity of cofilin, potentiating the generation of actin monomers [11]. Some of the more than 40 mammalian tropomyosin isoforms have an F-actin-stabilizing function, in which they compete with cofilin for F-actin binding. Surprisingly, however, certain tropomyosin isoforms may enhance cofilin recruitment and F-actin turnover [12].

Cortactin has its highest binding affinity to F-actin subunits containing ATP or ADP-P_i, thus protecting newly added subunits, whereas cofilin has its highest affinity for ADP-actin subunits, which accumulate in the more aged region of the filament. Because cofilin binding to F-actin enhances P_i (inorganic phosphate) release from neighboring subunits [13] and cortactin binding resists this, the balanced effect of cofilin and cortactin helps maintain the filament network and its dynamics at the leading edge of a migrating cell [14]. Cortactin is also an activator of the Arp2/3 complex, a seven-protein complex that binds along pre-existing filaments to nucleate new filament growth or capture filament pointed ends, creating 70° branch points. These branches provide the numerous filament barbed ends, the sites for actin assembly that drive membrane protrusion during polarized cell migration. In addition to cortactin, several proteins activated by transmembrane signaling, including neural Wiskott-Aldrich syndrome protein (N-WASp), have the ability to activate the Arp2/3 complex. In the highly specialized invadopodium compartment of metastatic cells, cofilin binds cortactin in a complex with Arp2/3, along with the Arp2/3 activator N-WASp and the N-WASp activator Nck1 (adaptor molecule with src homology domains 2 and 3) [15]. Cofilin is released for the essential function of severing after phosphorylation of a cortactin tyrosine [16]. Furthermore, as demonstrated only *in vitro*, cofilin can debranch the Arp2/3 complex by direct interaction [17], again suggesting that cofilin activity must be tightly regulated both spatially and temporally. In fact, the relationship between cofilin level and cell migration is biphasic [18]. A moderate increase in cofilin accelerates cell migration, clearly a factor in metastasis, but greater increases reverse this effect. Cofilin and its upstream regulators are essential to the development of cell polarity and to the maintenance of polarized cell motility [19-21].

Another leading-edge protein is coronin 1 (Crn1), which has three domains: an N-terminal β propeller domain that binds F-actin, a middle domain, and a C-terminal coiled-coil (CC) domain that modulates the Arp2/3 complex [22]. The β propeller and CC domains are involved in opposing effects on cofilin/actin interaction. Which effect prevails depends upon the nucleotide bound to actin [23]. The CC domain competes with cofilin in binding to ATP/ADP-P_i-actin, thus reducing the already weak binding of cofilin to this region of F-actin. In filament regions rich in ADP-actin, the β propeller domain synergizes cofilin severing. When the dominant inhibitory effects of the CC domain are negated by phosphorylation, Crn1 can switch from its filament-protective role to its cofilin-synergizing role via the β propeller domain.

Although *in vitro* studies of actin with one or two proteins have given us useful mechanistic information, a more complete picture of how the various proteins function *in vivo* is obtained when increasingly complex mixtures of purified proteins are used. In one such reconstituted system containing cofilin, Aip1, coronin 1a, and fluorescent actin, a new mechanism for cofilin depolymerization of single actin filaments was revealed [24]. F-actin disassembles in successive bursts not previously described and not observed with cofilin alone. Because cofilin has been shown to disrupt subunits between adjacent helical strands of actin in filaments [25] and Aip1 enhances cofilin severing and depolymerizing activity by binding along cofilin-decorated actin, one plausible mechanism suggested for the bursting activity is weakening of inter-filament strand interactions and the severing and removal of single-stranded actin subunits in a depolymerizing burst [24]. This 'cooperative strand separation' is supported by the fact that cofilin severing by itself does not alter the binding of the F-actin barbed-end capping protein (CapZ) but cofilin severing in the presence of coronin 1a and Aip1 abrogates CapZ binding. Unwinding of actin filament strands has been observed previously in electron micrographs, though not under the same conditions as used above [26]. However, interference with CapZ binding could arise from other mechanisms, so further studies are required to confirm the strand separation model.

New cellular functions of cofilin unrelated to actin-assembly regulation

Chaperoning actin to the nucleus

Actin itself has no nuclear localization sequence but cofilin does. Because actin has important functions in chromatin remodeling, formation of heterogeneous nuclear ribonucleoprotein complexes, and gene expression [27], the ability of cofilin to enable actin nuclear

functions is one of its crucial cellular roles. In higher plants, in which many different isoforms of ADF are expressed, *ADF9* deficiencies produced gene expression and chromatin remodeling phenotypes in addition to morphological and cytoskeletal defects reflecting *ADF9* cytoplasmic functions [28]. It is not known whether these nuclear functions require actin or are mediated by *ADF9* alone.

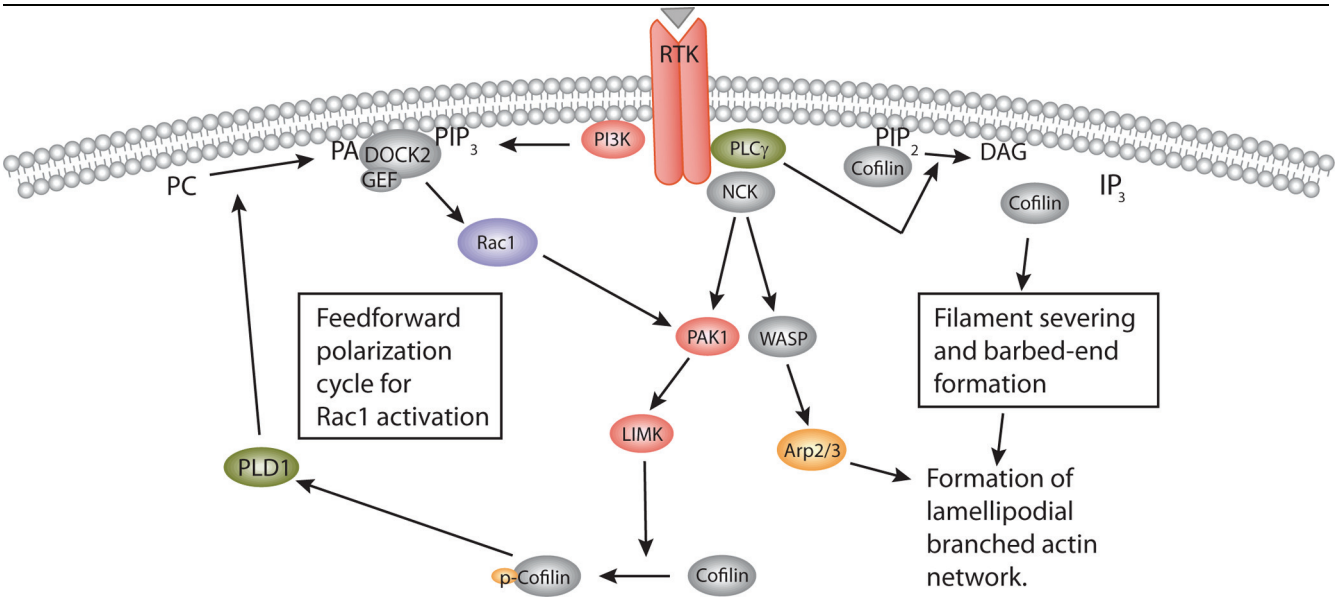
Release of mitochondrial cytochrome c

In lymphoma cells, cofilin oxidation and its mitochondrial translocation were found to induce apoptosis [29]. Cofilin translocation opens the mitochondrial permeability transition pore and releases cytochrome *c*, an early step in apoptosis. Neither the translocation to mitochondria nor the release of cytochrome *c* requires actin binding.

Activation of phospholipase D1

Cofilin phosphorylated on serine 3 is inactive in binding actin and has always been considered an inactive form. However, it was recently reported that phospho-cofilin can directly activate phospholipase D1 (PLD1) [30], an enzyme essential for chemotaxis of phagocytic cells (Figure 2). Investigation into the key role of cofilin in cell polarization (development of a leading edge) has previously focused on the release of active cofilin from its inhibition through binding phosphatidylinositol-4,5-bisphosphate (PtdIns4,5P_2) [1]. This lipid binding occurs in a multivalent manner and acts not only as a PtdIns4,5P_2-density sensor on the membrane [31] but also as a source of potentially active cofilin to generate actin barbed ends in response to signals that cause PtdIns4,5P_2 hydrolysis [14]. The activation of PLD1 by phospho-cofilin increases membrane phosphatidic acid, which is required for the activation of DOCK (dedicator of cytokinesis) proteins, a family of membrane-associated guanine nucleotide exchange factors for Rac1 [32]. Rac1 is also required for polarized cell migration. Because cofilin phosphorylation downstream of Rac1 (via PAK [p21-activated kinase] and LIMK [LIM kinase]) generates phospho-cofilin, this feed-forward

Figure 2. Possible roles of cofilin and phospho-cofilin in the establishment of the leading edge



In response to signaling through a receptor tyrosine kinase (RTK), phospholipase C gamma (PLCγ) is activated and hydrolyzes phosphatidylinositol-4,5-bisphosphate (PtdIns4,5P_2), releasing active cofilin from its inhibitory binding, allowing severing of capped quiescent filaments, and generating free barbed ends for driving assembly. Actin-related protein 2 and 3 (Arp2/3) complex is also activated via Wiskott-Aldrich syndrome protein (WASP) to set up the branched filament network driving forward protrusion of the membrane. The RTK also recruits phosphatidylinositol 3-kinase (PIK), generating PtdIns3,4,5P_3, which serves as a docking site for the binding of dedicator of cytokinesis 2 (DOCK2). The Rac1 guanine nucleotide exchange activity of DOCK2 is exposed only upon binding of the tail of DOCK2 to phosphatidic acid (PA). PA is generated from the hydrolysis of other phospholipids, such as phosphatidylcholine (PC), by the enzyme phospholipase D1 (PLD1), which is activated by P-cofilin. Active Rac1 activates the p21-activated kinase (PAK1), which activates the cofilin phosphorylation through LIM kinase (LIMK). This feed-forward cycle maintains active Rac1 at the leading edge but becomes self-limiting when cofilin phosphatases also are recruited or become active through downstream signals from these (e.g., inositol triphosphate [IP_3] → calcium → calmodulin → calcineurin → slingshot phosphatase) and/or other pathways. DAG, diacylglycerol; GEF, guanine nucleotide exchange factor; NCK, adaptor molecule with src homology domains 2 and 3; PIP_2, phosphatidyinositol diphosphate; PIP_3, phosphatidyinositol triphosphate.

cycle makes cofilin both an upstream activator and a downstream effector of Rac1 (Figure 2).

New modes of regulation

Phospho-tyrosine-dependent cofilin turnover

The phosphoregulation of ADF and cofilin on serine 3 is modulated by many transmembrane signaling pathways and their multiple regulatory kinases and phosphatases that converge on this site [1]. However, a recently identified src kinase phosphorylation site on cofilin (Y68), but not ADF (F68), provides another mode of cofilin regulation [33]. Phosphorylation of Y68 does not affect the actin-dynamizing activity of cofilin but does increase its ubiquitination and proteosome degradation to reduce total cofilin levels and cell spreading.

Oxidation

Cofilin is also regulated by oxidation of its four cysteine residues. In T cells, the generation of a C39-C80 intramolecular bond, delivered by the oxidative burst of granulocytes, does not eliminate the actin binding of cofilin but does increase F-actin [34]. Further studies were performed on the activity of cofilin oxidized with taurine chloramine, the primary oxidant generated by activated neutrophils [29]. Two intramolecular disulfide bonds form in cofilin in taurine-chloramine-treated lymphoma cells in which cofilin is a main target of oxidation. Neither disulfide bond alone inhibits cofilin-actin binding *in vitro*, but actin binding is eliminated when both internal disulfide bonds form. Furthermore, mutation of any one of these cysteines or serine 3 phosphorylation blocks cofilin's induction of cytochrome *c* release from mitochondria and inhibits the taurine-chloramine-induced apoptosis.

Future directions

It remains to be determined whether and exactly how the concentration dependence of active cofilin in actin turnover, stability, and nucleation contributes to the impressive spatial coordination of actin dynamics that underlies highly motile regions such as lamellipodia and neuronal growth cones. Many of the effects of cofilin previously ascribed to its direct modulation of actin may have to be reconsidered if PLD1 is also shown to have a role in mediating the process in question. Indeed, with cofilin being able to function in some cells as both an upstream activator and a downstream effector of Rac1 [10], the interpretation of results from many experiments inter-relating Rac1 and cofilin may need to be re-examined in light of this paradigm.

The transcriptional activity of plant ADF suggests that ADF/cofilins in animal cells may also regulate gene expression. Both mammalian ADF and cofilin have proven nuclear localization sequences and have been observed to accumulate in cell nuclei under some conditions. If their nuclear functions turn out to be independent of their ability to transport actin, target genes will need to be identified and many of the cytoplasmic effects of ADF/cofilin activation might need to be re-examined to determine whether they are independent of transcriptional events.

The src kinase phosphorylation of cofilin, but not ADF, enhances its ubiquitination and degradation and suggests a significant potential regulatory difference between cofilin and ADF in cellular processes involving src kinases. Indeed, some of the tumor cell line differences that have been observed in migration assays could result from different levels of ADF and cofilin [5]. Certainly, this regulatory difference suggests that a more detailed analysis of the specific levels of ADF/cofilin species is required when studying the roles of these proteins in cellular processes.

Cofilin plays an important role in the development and function of both neuromuscular junctions [35] and dendritic spines, the latter being the major excitatory synapses in the brain [36]. Cofilin regulation is critical for insertion of the AMPA family of glutamate receptors into the spine membrane, which give spines their functional plasticity important in memory and learning [37]. Understanding mechanistically how cofilin modulates cognition requires further study.

Finally, the newly discovered effect of phospho-cofilin on PLD1 activity suggests that additional work is needed to define the role of this enzyme and its cofilin dependence in different cellular processes. PLD1 is reported to be important in the alteration of membrane curvature during vesicle budding, endocytosis, and phagocytosis. Indeed, cofilin inhibition or knockdown has profound effects on the function and dynamics of the Golgi [38]; some may be due to actin regulation and others may be due to PLD1 regulation. It is of interest to determine whether cofilin phosphorylation through transmembrane signaling is important for the regulation of PLD1 in its many reported functions in cell migration and phagocytosis.

Abbreviations

ADP, adenosine diphosphate; ATP, adenosine triphosphate; ADF, actin-depolymerizing factor; Aip1, actin-interacting protein 1; Arp2/3, actin-related protein 2 and 3; CapZ, filamentous actin barbed-end capping protein; CC, coiled-coil; Crn1, coronin 1; F-actin, filamentous actin; N-WASp, neural Wiskott-Aldrich syndrome protein; P_i, inorganic phosphate; PLD1, phospholipase D1; PtdIns4,5P_2, phosphatidylinositol-4,5-bisphosphate.

Competing interests

The authors declare that they have no competing interests.

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