

Review Article

Focus on ADF/Cofilin: Beyond Actin Cytoskeletal Regulation

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Actin depolymerizing factor (ADF)/cofilin, an actin binding protein ubiquitously expressed in a variety of organisms, is required for regulation of actin dynamics. The activity of ADF/cofilin is dependent on serine 3 phosphorylation by LIM kinase (LIMK), which is regulated by the Rho small GTPase signaling pathway. ADF/cofilin is strongly associated with several important cell biological functions, including cell cycle, morphological maintenance and locomotion. These functions affect several biological events, including embryogenesis, oncology, nephropathy and neurodegenerations. Here, we focus on the biochemical and pathophysiological role of ADF/cofilin in mammals.

1. Introduction

ADF/cofilin has been reported to be involved in several cellular functions via regulation of actin dynamics. For instance, ADF/cofilin is required for actin reorganization at the contractile ring for cytokinesis and is essential for cell cycle progression. ADF/cofilin regulates actin dynamics through a depolymerization or severing of actin filaments. The only known mechanism for regulating the activity of ADF/cofilin activity is protein phosphorylation. ADF/cofilin becomes inactive when it is phosphorylated at serine 3 residue by LIM kinase (LIMK) or testis-specific kinase (TESK) 1 and 2 [1–3]. For LIMK, a series of signal transduction pathway for ADF/cofilin activity is primarily controlled by Rho family of small GTPase. Cells stimulated by growth factors lead to activation of the receptor tyrosine kinase (RTK) that recruits Rho small GTPase and Rho-associated protein kinase (ROCK) to phosphorylate LIM kinase and subsequent ADF/cofilin [4]. Also, dephosphorylation of ADF/cofilin is mediated by slingshot (SSH) phosphatase, chronophin (CIN) phosphatase, and protein phosphatase 1 and 2A (PP1 and PP2A) [5]. In addition to protein phosphorylation, the activity of ADF/cofilin is also regulated by intracellular pH and its association with phosphatidyl inositol bisphosphate (PIP2) [6].

Recent studies have shown that the activity of ADF/cofilin is increased at the telophase of mitosis to regulate the dynamics of actomyosin-based contractile ring and maintain the cleavage furrow for cell division [7, 8]. In addition to mitotic phase, optimal expression of ADF/cofilin is also critical for G1 to S phase progression. Forced expression of ADF/cofilin can result in G1 phase arrest through destabilization of actin cytoskeleton and upregulation of cell cycle inhibitor p27^{kip1} [9].

ADF/cofilin is involved in migration, locomotion and metastasis of cancerous cells. It has been reported that ADF/cofilin is associated with the advanced tumors that are prone to invasiveness and metastasis [10]. Therefore, targeting on ADF/cofilin is considered as one of the therapeutic strategies for cancer treatment [11, 12]. On the other hand, the inhibitory role of ADF/cofilin on cancer progression has also been reported because ectopic-expressed ADF/cofilin can suppress the motility and proliferation of human cancer cells [11, 13]. Thus, it remains controversial about the role of ADF/cofilin on tumorigenesis, and profound investigation would be required.

Taken together, ADF/cofilin is not only essential for cell motility but also the cell cycle progression. The phosphorylated state of ADF/cofilin affects the activity and stability of this protein on actin cytoskeletal organization

and subsequent cell physiology [14]. Furthermore, recent studies have addressed the importance of ADF/cofilin on neurology and nephrology [15, 16]. In this paper, we will discuss the biochemical mechanisms of ADF/cofilin. Also, the role of ADF/cofilin on mediating the physiology and pathology in neurology, nephrology, and oncology will also be elucidated.

2. Basic Functions of ADF/Cofilin

2.1. Actin Dynamics by ADF/Cofilin and Other Actin-Binding Proteins. The ADF/cofilin family includes three isoforms of proteins, the so-called cofilin-1, cofilin-2, and destin (also named ADF). They share similar biochemical functions on regulating the actin dynamics. Cofilin-1 is ubiquitously expressed in nonmuscle tissues of various organisms, while cofilin-2 is only expressed in muscle. ADF is also expressed in non-muscle tissues, but the level is about 5% to 10% of cofilin-1 [17]. The name of cofilin was obtained from its binding ability on monomeric actin embedded in the actin filaments (Co-filamentous with actin) with a 1 : 1 stoichiometry [6].

Regulation of actin dynamics by ADF/cofilin is largely dependent on the concentration of ADF/cofilin *in vitro* and *in vivo* [6]. Lower concentration of ADF/cofilin exhibits higher binding affinity to ADP-bound actin in the filaments. The consequence is to promote depolymerization from the pointed end of actin filaments. On the contrary, higher level of ADF/cofilin can stabilize the actin filaments and even initiate the nucleation of G-actins, which lead to elongation and branched by profilin or Arp2/3 complex, respectively [6, 18, 19]. Therefore, the level of ADF/cofilin can influence the actin dynamics with a biphasic manner that may trigger different effects on cell physiology [20].

ADF/cofilin not only severs or depolymerizes actin filaments but also cooperates with other actin-binding proteins to assemble stress fiber and lamellipodia formed by filamentous actin [21, 22]. Formation of stress fibers and lamellipodia is regulated by Rho signaling pathway, which mediates various downstream kinase activity to phosphorylate ADF/cofilin, tropomyosin, and light chain of myosin II (MLC) [23]. For stress fibers formation through Rho, ADF/cofilin is inactivated through phosphorylation by LIMK1, while myosin II becomes active via phosphorylation by myosin light chain kinase (MLCK). For lamellipodia formation at the leading edge, the ADF/cofilin activity is increased by dephosphorylation through phosphatases. By contrast, the myosin II activity is decreased after dephosphorylation [24–26]. Therefore, ADF/cofilin alone is not sufficient to mediate actin cytoskeletal organization. A cooperation of ADF/cofilin with other actin-regulating proteins is required for normal mechanical functions in cells.

2.2. The Signal Transduction Pathways for Regulation of ADF/Cofilin Activity and Actin Filaments Reorganization. The reorganization of actin filament is triggered by extracellular signals such as growth factors, chemoattractants, or toxins

that may bind to surface receptors. These receptors turn on a series of signal transduction pathways, such as Akt-phosphoinositide 3-kinase (PI3K) and Ras-Erk cascades after mitogenic stimulations [27–30]. Rho small GTPase family and its downstream effectors, including Rho-associated kinase (ROCK) and p21-activated kinase (PAK), are responsible for forming and organizing the actin cytoskeleton into filopodia, lamellipodia, and stress fibers. Both activated ROCK and PAK phosphorylates activate LIM kinase (1/2) and then inactivate ADF/cofilin via phosphorylation at serine 3 residue [1, 31, 32]. Another kinase named TESK can inactivate ADF/cofilin through phosphorylation at the same residue [2]. The protein kinase domain of TESK is similar to that of LIM kinase, although their overall structures are distinct. It has been demonstrated that regulation of ADF/cofilin activity by TESK is dependent on integrin [2]. Thus, at least two parallel pathways may exist for regulation of ADF/cofilin activity [2, 33]. In contrast, slingshot (SSH) phosphatase and chronophin (CIN) have been identified to activate ADF/cofilin by dephosphorylating serine 3 residue and suppressing the assembly of actin filaments [34, 35].

Although the activity of ADF/cofilin on actin regulation has been widely studied, the expression level of ADF/cofilin is less reported. We have found that ADF/cofilin is accumulated in confluent cells, and overexpression of ADF/cofilin causes G1 phase arrest in a variety of cell lines [9]. A recent report shows that the protein stability of ADF/cofilin is dependent on the phosphorylation of tyrosine 68 residue by v-src protooncogene [36]. Overexpression of v-src has been reported to influence F-actin organization and cell spreading in cancerous cells [37, 38]. It is of interest to further investigate whether ADF/cofilin is required for v-src-mediated cell proliferation and migration.

3. ADF/Cofilin in Cell Cycle and Embryogenesis

3.1. ADF/Cofilin and Cell Cycle. The cell cycle progression is accompanied by a reorganization of actin cytoskeleton that mediates the morphological change and cell spreading for conveying the extracellular stimuli to intracellular signal transduction. It has been reported that ADF/cofilin also plays an important role during cell cycle [39, 40]. Cell anchorage and spreading are observed in the interphase, while the morphology becomes round and loss of attachment from the substratum after cells enter the mitotic phase [41, 42]. In the mitotic phase, actin filaments are also involved in chromosome segregation by anchoring onto the microtubules [43]. The effects of ADF/cofilin on cell cycle include (1) providing the mechanical force for division of daughter cells during cytokinesis and (2) regulating the actin dynamics for signal transductions in the G1 phase [44, 45]. To regulate the actin dynamic during mitosis, the ADF/cofilin activity is suppressed by LIMK 1 and 2 in the metaphase [46, 47], but reactivated by slingshot homolog 1 (SSH-1) phosphatase after the telophase [7]. Overexpression of LIMK1 has also been reported to increase the aneuploidy and chromosomal instability in prostate cancer, suggesting that ADF/cofilin activity is importance for cell division [48]. We have found that forced expression of cofilin-1 leads to

G1 phase arrest [39]. Recently, we also found that cofilin-1 expression is lowest in G1 phase compared to other cell cycle phase (unpublished data). Thus, the expressions as well as the activity regulation of ADF/cofilin are both essential for the cell cycle progression.

Growth factors affect the cell proliferation by stimulating different signal transduction pathways, including Akt -PI3K, Ras-MAPK (mitogen activated protein kinase), and small GTPase family, Rho, Rac and Cdc42 [49–51]. It has been reported that the upregulation of cyclin D1, suppression of p21^{cip1/waf1}, and hyperphosphorylation of retinoblastoma protein (Rb) are involved in G1 to S phase transition via activation of Ras-MAPK and small GTPase family pathways [52, 53]. Upon stimulation, the activity of ADF/cofilin is ablated by the Rho signaling pathway for actin cytoskeletal reorganization in the G1/S phase progression [1, 9, 54]. However, the MAPK activity was not influenced by over-expressed cofilin and cytochalasin B, a routinely used actin targeting agent (unpublished data), suggesting that directly destabilization of actin cytoskeleton is sufficient to ablate the cell cycle progression even the cells are stimulated by mitogens.

3.2. ADF/Cofilin and Embryogenesis. The embryogenesis is associated with cell cycle progression to become a multi-cellular entity [55]. The developing stages of embryogenesis include zygotes, morula, blastomeres, and gastrula. The zygote is the first stage of embryogenesis followed by the morula, blastomeres (also called blastocyst in mammalian), and gastrula in the end. After gastrula, the developments of ectoderm, mesoderm, and endoderm are initiated by rapid cell division. Actin cytoskeletal organization is involved in cell divisions for determining the cell polarity, orientation, and proliferation in embryos, as well as the development of cell walls in higher plants [56, 57]. Deactivation of ADF/cofilin is critical for the compaction stage, which is a process in 8-cell stage of embryos [58]. The asymmetry of embryos is first observed in 8-cell stage when operates the polarization, flatness, and adherent junction of embryos within blastomeres. These processes can only be promoted when the expression of ADF/cofilin is silenced during this stage. Knockdown or inactivation of ADF/cofilin using siRNA or site-directed mutagenesis accelerates the compaction of embryos, respectively [58]. This report demonstrated that the level of ADF/cofilin needs to be precisely regulated for cell cycle progression and embryogenesis.

4. ADF/Cofilin in Neurology, Nephrology, and Cancer

ADF/cofilin also plays an important role on neuron development, kidney functions, and cancer development. ADF/cofilin has been identified as a biomarker of Alzheimer's disease [59]. In addition, ADF/cofilin is regarded a critical molecule for providing the mechanical force on the filter barrier system in podocytes, which are specialized visceral epithelial cells in a glomerulus [16]. Also, ADF/cofilin may be involved in advanced human cancers with the metastatic

property [11]. We briefly summarize the biochemical and biological role of ADF/cofilin on these human disorders.

4.1. ADF/Cofilin and Alzheimer Disease. It has been reported that the appearance of cofilin-actin rod-enriched inclusion bodies is a pathological feature widely existed in a broad spectrum of neurodegenerative diseases [15, 59]. Cofilin-actin rods are rapidly formed in response to neural stress [60]. ADF/cofilin can be activated by the neurodegenerative stimuli, such as aggregated beta-amyloid ($A\beta$) and oxidative stress. ADF/cofilin abnormally aggregates punctuates and rod-like linear arrays along the striated neuropil threads, which is a conventional feature of Alzheimer disease [61, 62]. Furthermore, ADF/cofilin undergoes phosphorylation and dephosphorylation stimulated by $A\beta_{1-40}$ and $A\beta_{1-42}$ in neurons, respectively [63]. The phosphoregulation of ADF/cofilin protein further influence the formation of rod-like actin bundles and the accumulation of phosphorylated tau protein, a critical pathological characteristic of Alzheimer disease. Hence, ADF/cofilin is likely a mediator to cause Alzheimer disease by increasing several transport defects in neurons responding to environmental stress [63]. Taken together, ADF/cofilin is prominent in hippocampal and cortical neurites of the postmortem brains of Alzheimer's patients, especially in neuritis with amyloid beta depositions [61].

4.2. ADF/Cofilin Is Critical for the Filter Barrier System of Kidney. The role of ADF/cofilin in nephrology has also been defined in last decade. Currently, it is believed that the active form of ADF/cofilin is not only critical for maintaining the morphology of podocytes but also required for the development of podocytes [64]. Podocytes are high-specialized and terminal-differentiated epithelial cell located at the outer aspect of the glomerular basement membrane to prevent the leakage of urine protein, maintenance of glomerular capillary loops integrity, and serve as a barrier to against the intracapillary hydrostatic pressure [65, 66]. Podocytes consist of three segments with different functions: a cell body, major processes, and foot processes. The processes are mainly organized by actin dynamics [67]. The actin filament-mediated mechanical force and focal adhesion in podocytes are important for maintaining the functions of selective filtration barrier of kidney. Foot processes (FP) have three functionally membrane domains: the apical membrane domain, the slit diaphragm (SD), and the basal membrane domain (or sole plate) associated with glomerular basement membrane (GBM). These structures form the adherent junctions and barrier to filtrate protein and albumin from blood vessels and capillaries around the glomerulus [68, 69]. Also, the actin cytoskeleton is critical for all three functional domains [16, 67]. Inactivation of ADF/cofilin by serine-3 phosphorylation is reported to be correlated with proteinuria in zebra fish, mice, and humans [70]. Proteinuria is a type of nephropathy caused by the injury of three cell types including mesangial cells, podocytes, and endothelial cells in glomerular units. Degeneration of podocytes is a primary event in the development of chronic renal failure and proteinuria. Activated ADF/cofilin

is well distributed in normal podocytes, but inactivated (phosphorylated) ADF/cofilin can be found throughout misfunctional podocyte cells [70]. Of interest, ADF/cofilin can be activated for actin filament reorganization through receptor tyrosine kinase activation, the so-called Nephrin-Neph1 receptor complex on the membranes of podocytes [64]. In addition to ADF/cofilin, α -actinin-4 [71], nephrin [72], and podocin [73] are also involved in regulating the dynamics of actin cytoskeleton and are important for the functions of podocytes on renal filtration.

4.3. ADF/Cofilin in Cancer Growth and Metastasis. The features of cancers include uncontrollable growth and distant dissemination. They are important index for design of cancer therapeutic strategies. The actin cytoskeletal reorganization is involved in these phenotypes, and several toxins targeting on the networks of actin filaments have been reported to efficiently inhibit cell cycle progression and induce apoptosis in cancer cells [74, 75]. For instance, cucurbitacins [76, 77] derived from medicinal plants have many isoforms and they are widely used in cancer therapy because they disrupt the formation of filamentous actin and subsequently cause G2/M phase arrest and apoptosis in breast cancers [78], glioblastoma (GBM) [79], and prostate cancer [80]. In addition, a series of actin toxins that display highly antitumor effects have been used for anticancer researches by interfering the actin polymerization and depolymerization. For instance, latrunculin A (LA) has been used for inhibition of gastric cancers [81]; cytochalasin B (CB) is able to control the growth of lung cancers [82], and jasplakinolide (JP) can inhibit the prostate cancer and Lewis lung cancer [83]. LA can induce cofilin-1 phosphorylation, but the mechanisms are largely unknown [84]. In our lab, we have demonstrated that overexpressed cofilin-1 enhances radiosensitivity and G1 phase arrest in human lung cancer cells [39, 85]. Overexpressed cofilin-1 is normally phosphorylated and is able to repress the expression of several DNA repair proteins including Rad51, Ku70, and Ku80. For the G1 phase arrest, cofilin-1 may upregulate the cell cycle inhibitor p27^{kip1} through transcriptional and translational mechanisms [9]. Whether cofilin-1 can be used for gene therapy to avoid high toxicity of actin toxins is of interest to further investigate.

The distant metastasis of tumor cells is the primary cause of mortality. Metastasis and invasion are caused by multiple processes that are associated with the reorganization of actin filament as well as actin regulatory proteins, such as ADF/cofilin, Arp2/3 (actin-related proteins 2/3), and WASP (Wiskott-Aldrich syndrome protein) [18, 20]. The cancer migration and metastasis are suppressed when ADF/cofilin is silenced by the small interfering RNA (siRNA) [11, 86, 87]. Because overexpression of LIMK1 has been reported in different types of human cancers, it seems reasonable that ADF/cofilin should be activated in cancer metastasis. [88–91]. On the other hand, overexpression of ADF/cofilin inhibits motility and invasion in different types of cancer cells [13, 92]. Thus, the role of ADF/cofilin on invasion and metastasis required further investigation. In addition, in the epidermal-growth-factor- (EGF-) induced migration, the activity of ADF/cofilin is regulated by phospholipid

PtdIns(4,5)P2 (PIP2) and phospholipase Cy (PLC γ) that induce transient activity of ADF/cofilin last for 60 second after EGF stimulation [93]. At least two signal transduction pathways may regulate the activity of ADF/cofilin through phosphorylation on serine 3 residue during cell migration.

5. Conclusion

ADF/cofilin regulates actin dynamics and influences various biological functions in different cell types. Deregulation of ADF/cofilin in amount or activity may be associated with human diseases. The activity and stability of ADF/cofilin have been reported to be controlled by the Rho small GTPase and Src signaling pathway, respectively. Thus, targeting on these signaling pathways would be one of the important strategies for cancer treatment. ADF/cofilin is also associated with Alzheimer's diseases and proteinuria, while it is a cause or consequence of these disorders required further investigations. Although it is believed that ADF/cofilin is associated with cancer development, how ADF/cofilin participates malignancy is not fully understood. We expect that the pathophysiological function of ADF/cofilin will be better understood by more comprehensive studies in the future.

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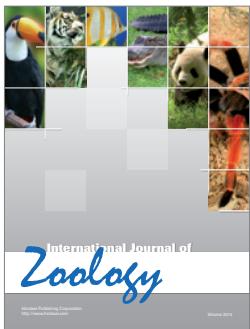
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