Cofilin Signaling

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Contributor: Asim Bepari , Jannatun Namme

Three ADF/cofilin family members are expressed in mammals: ADF, cofilin-1, and cofilin-2. The first member ADF (also known as destrin), encoded by the gene DSTN in humans, was initially identified in the chick brain. Cofilin was discovered as an actin-interacting protein in the porcine brain. Later, Ono et al. identified two mammalian variants of cofilin, non-muscle type (also known as cofilin-1 and n-cofilin) and muscle type (also known as cofilin-2 and m-cofilin). In humans, cofilin-1 and cofilin-2 are encoded by the genes CFL1 and CFL2, respectively. Different isoforms of ADF/cofilin have qualitatively similar but quantitatively different effects on actin dynamics. To be noted, both ADF and cofilin show cooperative binding with actin filaments. Interestingly, cofilin-1 comprises almost 90% of the total ADF/cofilin family in CNS.

Cofilin can bind to both G-actin and F-actin, exhibiting stronger affinities for the ADP-bound actins than the ATP- or ADP-Pi-bound forms. Cofilin binding to F-actin induces actin subunit rotation, enhances Pi release along the filament, and promotes filament severing in a concentration-dependent manner.

cofilin   cofilin-1   cytoskeleton   neurodegeneration   actin   neuron

Alzheimer's disease   schizophrenia   LIMK1   SSH1

1.Introduction

Neurons contain a cytoskeleton consisting of microtubules, neurofilaments, and actin filaments. Microtubules are composed of tubulin proteins and other polypeptides and provide the essential organization of organelles. Neurofilaments, which are class IV intermediate filaments, offer structural support to axons and influence nerve conduction velocity. Actin filaments (F-actin) are composed of globular actin monomers (G-actin). Dynamic transition can occur between G-actin and F-actin, and the polymerization-depolymerization events are spatiotemporally regulated in response to numerous extracellular and intracellular stimuli. Actin is an ATPase, and both G-actin and F-actin can bind to ATP. When ATP-bound G-actin monomers assemble into a polymer, ATP hydrolyzes rapidly to generate ADP-Pi actin, slowly releasing the inorganic phosphate producing ADP-actin subunits. Consequently, actin filaments exhibit considerable asymmetry with a plus end (barbed end or growing end) and a minus end (pointed end or shrinking end) dominated by ATP- and ADP-actins, respectively. ATP-G-actin monomers are preferentially polymerized to the barbed end whereas, ADP-actin subunits are depolymerized from the pointed end. The actin dynamics is precisely controlled by various actin-binding proteins (ABPs) such as actin-related protein 2/3 complex (Arp2/3), cortactin, formin, profilin, and actin-depolymerizing factor (ADF)/cofilin (reviewed in [1]).

Three ADF/cofilin family members are expressed in mammals: ADF, cofilin-1, and cofilin-2 (reviewed in [2][3]). The first member ADF (also known as destrin), encoded by the gene DSTN in humans, was initially identified in the chick brain [4]. Cofilin was discovered as an actin-interacting protein in the porcine brain [5][6]. Later, Ono et al. identified two mammalian variants of cofilin, non-muscle type (also known as cofilin-1 and n-cofilin) and muscle type (also known as cofilin-2 and m-cofilin) [7]. In humans, cofilin-1 and cofilin-2 are encoded by the genes CFL1 and CFL2 , respectively. Different isoforms of ADF/cofilin have qualitatively similar but quantitatively different effects on actin dynamics [8]. To be noted, both ADF and cofilin show cooperative binding with actin filaments [9][10]. Interestingly, cofilin-1 comprises almost 90% of the total ADF/cofilin family in CNS [11]. For simplicity, we will use the term 'cofilin' to mention cofilin-1 hereafter.

Cofilin can bind to both G-actin and F-actin, exhibiting stronger affinities for the ADP-bound actins than the ATP- or ADP-Pi-bound forms [12]. Cofilin binding to F-actin induces actin subunit rotation, enhances Pi release along the filament, and promotes filament severing in a concentration-dependent manner [8][13][14]. Severing is rapid at a low cofilin/actin ratio and suppressed at a high cofilin/actin ratio. Interestingly, only a few cofilin molecules can induce actin filament fragmentation, predominantly at the pointed end of the cofilin domain [15][16]. Severing generates newer ends of the filament where cofilin may accelerate the disassembly of ADP-actins from the pointed end [16]. On the contrary, higher cofilin concentrations can favor actin polymerization through nucleation [13]. Thus, cofilin is capable of controlling actin dynamics through both polymerization and depolymerization.

Conceivably, regulation of cofilin activity is immensely complex where diverse stimuli in the cell microenvironment orchestrate the cytoskeleton dynamics in physiological and pathophysiological conditions [17][18]. For instance, two guidance cues, nerve growth factor (NGF) and netrin-1, were found to activate cofilin, increase free actin barbed ends, and promote growth cone protrusion [19]. Meyer et al. (2005) showed that insulin-like growth factor I (IGF-I) enhances neuroblastoma cell motility through activation of cofilin and its upstream regulators [20]. Tilve and colleagues (2015) observed an extracellular synuclein-induced cofilin inactivation and dysregulation of neuronal actin dynamics [21]. At the molecular level, cofilin activity is modulated by phosphorylation-dephosphorylation, binding to other regulatory proteins, and redox modifications. We have discussed essential cofilin regulators in the next section. For further details, interested readers are referred to many outstanding reviews describing the roles and regulations of cofilin in actin dynamics [22][23][24][25][26][27].

2.Signaling Mechanisms for Cofilin Activation and Inactivation

The Ser-3 residue in cofilin is a conserved phosphorylation site [28][29]. Cofilin is activated via dephosphorylation at Ser-3 by slingshot family proteins (SSHs; SSH1, SSH2, and SSH3) through the Ca 2+ /calmodulin-dependent calcineurin activation pathway [30][31]. On the other hand, cofilin is deactivated via phosphorylation at Ser-3 by LIM domain kinases (LIMKs) and dual-specificity testis-specific protein kinases (TESKs) [32][33].

TESKs are structurally related to LIM-kinases with a kinase domain and a unique C-terminal proline-rich domain. TESK1 can phosphorylate cofilin at Ser-3 in vitro and in vivo to affect actin organization [34]. When active cofilin

was expressed in HeLa cells, rhodamine-phalloidin (a conjugate dye used to stabilize actin filaments in vitro) staining was markedly decreased by cofilin-mediated actin depolymerization, and this phenomenon was reversed by co-expression of TESK1 with cofilin [35]. Using TESK1 knockout mice, Wang et al. (2018) showed that TESK1 kinase activity is critical in cofilin-induced actin depolymerization [36]. TESK2 was also found to mediate cofilin phosphorylation and the formation of actin stress fibers in cultured cells [37].

CAPs are multi-domain actin-binding proteins having the capability of actin dynamics regulation at multiple levels [38]. CAPs and cofilin synergize to enhance depolymerization of F-actin at the pointed end [39]. CAPs compete with cofilin to bind with G-actin and promote its nucleotide exchange. Though two homologs of CAPs, CAP1 and CAP2, have been described in mammals, in humans, CAP2 plays a crucial role in neuronal cells, most notably in spine morphology [40]. CAP2 dimers/oligomers promote depolymerization of cofilin-saturated fragments of F-actin [39][38]. Alterations in dendritic architecture and spine morphology have been reported in CAP2 knockout neurons [41]. A recent study reported CAP2 as a postsynaptic protein relevant to regulating synaptic transmission and plasticity by shaping dendritic and spine morphology, which are all interconnected to actin depolymerization through cofilin activity [41].

In addition to phosphorylation-dephosphorylation, cofilin activity is also altered by several other mechanisms, including redox regulation. ROS can directly modulate cofilin in two different ways. First, direct oxidation of cofilin at Cys-139/147 to sulfenic acid in response to hydrogen peroxide (H_2O_2) impairs cofilin binding to actin [42]. Second, under mild oxidative stress, ROS induces cofilin activation and an intermolecular disulfide bond between Cys-147 and Cys-39, forming cofilin-actin oligomers [43][44] and may lead to rod formation under an oxidative environment. Nonetheless, ROS can modulate cofilin by oxidation and inhibiting its actin-severing action.

3.Cofilin Functions in the CNS Development

Neurulation in human embryos proceeds in two phases, primary and secondary. The neural tube, the embryonic precursor of the CNS, is developed from the neural plate (a section of the ectoderm) via primary neurulation [45] involving four overlapping stages: neural induction, shaping, bending of the neural plate, and neural tube closure [46]. Neural crest cells are generated from the neural tube during neurulation and take long migration routes before settling and differentiating into distinct cell types. Gurniak et al. (2005) showed that the cofilin-mutant mouse embryos fail to form the neural tube and exhibit substantial aberration migration of neural crest cells [47]. Cofilin mutation results in malformation of actin structure and loss of polarity of the neural crest cells, which severely affects neuronal development in mice [47]. Cofilin is indispensable for actin depolymerization and actomyosin organization in the neural epithelium, which are critical for neural tube formation [48][49]. A lack of secretory pathway calcium ATPase (SPCA1) in mouse embryos shares similar neural tube deformation with cofilin mutants [50]. Interestingly, SPCA1 was found to direct cofilin colocalization with apical actin filaments in the neuroepithelium. Thus, cofilin appears as an essential protein for proper neural tube closure during embryonic development.

The formation of neurites, the immature projections arising from the neuronal cell body, is a unique and significant step in neurogenesis. The brain's development and function largely depend on neurite formation, which requires

many growth signals, receptor stimuli, and a complex interplay among intracellular and extracellular signals. Actin can function as a microtubule entry barrier in dendritic spines and guide microtubules growing into filopodia [51]. Penetration of microtubules is determined by an adequate balance between forward polymerization and backward transport by the retrograde flow of lamellipodium actin [52]. Three steps are involved in axon elongation: protrusion, engorgement, and consolidation. In protrusion, F-actin's polymerization triggers elongation of lamellipodia and filopodia, whereas F-actin depolymerization guides polymerized microtubules to elongate into the peripheral domain. In the consolidation step, the transition of microtubules from polymerization to stabilization enables the formation of the neurite shaft. Repeated cycles of these three steps lead to axon elongation. Again, the growth cone's lamellipodial extension and filopodial retraction are necessary for all three axon elongation stages [52]. Cofilin is highly concentrated in dendritic spines and growth cones of neurons [53]. It controls the number and length of filopodia in response to brain-derived neurotrophic factor (BDNF) [54]. At the rear of actin meshwork in the growth cone, cofilin promotes actin monomers' recycling to the leading edge for assembly. Cofilin thereby enhances membrane protrusion by altering interactions of F-actin with microtubules [55]. Cofilin also facilitates bundling and penetration of microtubules into the growth cone and restricts microtubule entry into dendritic spines.

Furthermore, several proteins such as neuronal Nogo-A, semaphorin 3A, and BDNF have been found to regulate the growth cone through cofilin [55][56]. Overexpression of cofilin or its phosphorylation-resistant mutant cofilin S3A (active cofilin mutant) can stimulate more growth cone-like waves, which produce significantly longer axons. In contrast, the inactivation of cofilin by LIMK1 overexpression disrupts the fan-like structure of the growth cone, perturbing axon elongation and growth cone motility [57][58]. Such defects can be recovered by overexpressing S3A or slingshot homolog (SSH), a protein phosphatase [59]. Enhancement of actin filament turnover in vivo is critically regulated by cofilin during neurite formation. Cofilin knockout mice exhibit severe abnormalities in multiple brain regions resulting from a profound retrograde flow reduction [57].

Axonal distortion following external or internal injury or inflammation in the CNS ensues neurodegeneration. Ironically, a failed regeneration of injured axons in the adult CNS is contrasted with the vigorous axonal growth during embryonic development. Regeneration failure is associated with extracellular inhibitory factors and downregulation of neuron-intrinsic regenerative programs (reviewed in [60][61]). Unlike the developing neurons, injured CNS neurons do not display growth cones following axon injury [62]; instead, dystrophic bulbs called 'retraction bulbs' are generated.

4.Cofilin Dysregulation and Neurodegenerative and Psychiatric Disorders

An appearance of amyloid-beta (Aβ)- and tau-dependent spine loss is a pathologic feature that directly correlates with cognitive declines in AD [63]. Cofilin was found to aggregate with Aβ oligomers in human AD brain tissues and mouse AD models [11][64]. Aβ interacts with many synaptic proteins such as NMDA receptors, PrP C (prion protein), ephrin type B-2 receptor (EphB2), metabotropic glutamate receptor 5 (mGluR5), and β-integrin [65]. Woo et al. (2015) showed, using both cultured neurons and in vivo mouse models, that the ran-binding protein 9 (RanBP9) can mediate the accumulation of cofilin-actin rods [66]. RanBP9 enhanced the PrP C-dependent Aβ-β1-integrin

signal and cofilin dephosphorylation by SSHs. The RanBP9-SSH1-cofilin axis promoted cofilin translocation in the mitochondria and induced a cofilin-actin pathology leading to synaptic and mitochondrial dysfunction [66][67]. Decreased cofilin expression by downregulation of RanBP9 resulted in protection from memory and learning defects in a mouse model of contextual fear conditioning, signifying roles of cofilin activity levels in hippocampal learning and memory [66].

Decreased CAP2 and increased cofilin levels were reported in hippocampal postsynaptic fractions in an AD mouse model [68]. Small hairpin RNA (shRNA)-mediated down-regulation of CAP2 altered dendritic and spine morphologies in cultured neurons. Additionally, induction of LTP in rat hippocampal neurons augmented CAP2 dimerization and CAP2-cofilin association. This study also found a decreased hippocampal CAP2 protein level and a reduction in the ratio of CAP2/cofilin in AD patients compared to healthy controls, implicating CAPs in AD pathophysiology [68].

Immediately after ischemic stroke, neuronal cell death occurs rapidly due to initial loss of blood flow, increased oxidative stress by an overload of cytosolic Ca 2+ , increased excitotoxicity, lack of oxygen, and glucose. Overload of Ca 2+ activates NADPH-oxidase (NOX) through PKC and nitric oxide (NO), leading to a high level of glutamate accumulation in extracellular space (reviewed in [69][70]). Glutamate causes excitotoxicity at higher doses by overstimulating NMDA, AMPA receptors, Ca 2+ overload, and mitochondrial dysfunction [71]. Several studies reported that both non-NMDA and NMDA receptors can stimulate glutamate-induced cofilin dephosphorylation and rod formation [72][73][74]. During excitotoxic neuronal death, NMDARs stimulation promotes cofilin dephosphorylation by the Ca 2+ -SSH1-cofilin pathway in cortical neurons where cofilin physiologically remains phosphorylated. NMDA-induced cofilin dephosphorylation enhances cofilin translocation in mitochondria and decreases p-cofilin level in the cytosol. Cofilin contributes to the translocation of Bax into mitochondria. [75], promoting mitochondrial membrane depolarization and releasing apoptotic factors like cytochrome C. Acute knockdown of cofilin or SSH1 exhibited a marked neuroprotective action on NMDA-mediated neuronal death [75]. Another recent study demonstrated that rod-induced microtubule-associated protein-2 (MAP2) degradation and cofilin-mediated apoptosis are reduced if cofilin is inhibited by LIMK1 overexpression in the infarct cortex after stroke [76].

Moreover, cofilin oxidation may lead to oxidant-induced apoptosis [77]. Ischemic and hemorrhagic stroke-induced oxidative stress might be a consequence of ROS-induced cofilin oxidation, which enhances translocation of free cofilin into the mitochondria, thereby initiates cytochrome C release leading to apoptosis [78]. During the acute phase of ischemic injury and the initial phase of secondary injury to intracranial hemorrhage (ICH), inhibition of elevated cofilin activation in the extracellular region either using pharmacological inhibitor or via phosphorylation could diminish excitotoxicity-induced neuronal death (reviewed in [79]).

5.Conclusions

The findings generated from a plethora of studies implicate that proper balance in cofilin activity is a prerequisite for actin turnover and CNS functions. Among various regulatory pathways already discovered for cofilin, phosphoregulation through SSHs and LIMKs is the most critical mechanism, where the Ser-3 residue of cofilin is

the specific target. Roles of cofilin Cys-39 and Cys-147 residues are also becoming apparent in the context of ROS-induced rod formation in many neurodegenerative disorders. Newer studies report different molecular pathways of cofilin through which cofilin dysregulation and translocation in subcellular regions might be associated with various CNS disorders.

Recent advances in experimental techniques will significantly facilitate the understanding of the signaling pathways of cofilin function in development and disease conditions. Drugs or peptides targeting the critical amino acid residues of cofilin might be a new potential therapeutic strategy for neurodegenerative disorders.

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