Profilin, a multi-modal regulator of neuronal plasticity

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Summary

Thirty years after its initial characterization and more than 1000 publications listed in PubMed describing its properties, the small (ca15 kDa) protein profilin continues to surprise us with new, recently discovered functions. Originally described as an actin-binding protein, profilin has now been shown to interact with more than a dozen proteins in mammalian cells. Some of the more recently described and intriguing interactions are within neurons involving a neuronal profilin family member. Profilin is now regarded as a regulator of various cellular processes such as cytoskeletal dynamics, membrane trafficking and nuclear transport. Profilin is a necessary element in key steps of neuronal differentiation and synaptic plasticity, and embodies properties postulated for a synaptic tag. These findings identify profilin as an important factor linking cellular and behavioural plasticity in neural circuits. ***BioEssays*** **30:994–1002, 2008.**

Introduction

Profilin was identified as an actin-binding protein in calf thymus over 30 years ago,[1] but soon found in all other organisms where it has been searched for. In mammals, profilins are a group of genes, ranging from the well-described ubiquitously expressed profilin I and the brain-specific profilin II to the recently discovered and poorly described testis-specific profilins III and IV.[1–4]

Interestingly, while profilin IV appears to be evolutionary conserved (being found from vertebrates all the way down to some simple unicellular organisms), profilin II is likely to have been derived relatively recently in vertebrate evolution from profilin I.[5] In general, profilins from different organisms exhibit only moderate sequence similarity, but nevertheless show remarkably conserved structures and functions[6,7] (Table 1, Fig. 1). Many of the early experiments focussing on profilin's ability to regulate actin filament assembly have been carried out with profilins from different sources, but their functional conservation suggests that profilins share basic properties across phyla and isoforms.

Profilin binds actin with a K_d in the micromolar range[8,9] and in vitro studies showed that it interferes with actin filament nucleation, one major reason for its initial description as an actin-sequestering protein inhibiting actin filament formation. This view changed dramatically over the years, starting with the notion that profilin catalyzes nucleotide exchange on actin[9] and can govern actin monomer addition to preformed actin filaments.[10] This led to the model that profilin's main function in filament assembly is to add ATP-actin monomers to the growing end of the actin filament.[10–12] A pure sequestering function in vivo is also unlikely given the relative concentrations of actin and profilin in cells.[13] Finally, the identification of actin-regulating proteins other than profilin and their suggested functions based on biochemical and structural data increased the need for a suitable model to test contributions of these proteins to actin filament assembly. This model was delivered by the development of in vitro reconstitution assays of bacterial motility (Fig. 2). Adding low concentrations of profilin to the protein mix increased actin-based bacterial motility.[14] However, profilin concentrations showing a stimulatory effect on actin filament assembly were in the nanomolar to low micromolar range, with micromolar concentrations not further increasing motility. In motile mammalian cells, reported profilin concentrations are in the range of 10–150 μM.[13,15,16] In vitro experiments on actin assembly in the presence of 10–100 μM profilin showed that profilin can depolymerize actin filaments and compete with certain filament-capping proteins.[17] Consequently, high profilin concentrations (estimated to be between 11–22 μM) injected into mammalian cells infected with Listeria slowed down rather than enhanced bacterial motility.[18]

In addition to its role as an actin binder, profilin was found to interact with phosphatidylinositides, with great preference for phosphatidylinositide-4,5-bisphosphate (PIP2).[19,20] Profilin binding inhibits hydrolysis of PIP2 by phospholipase C and thus has the potential to interfere with another intracellular

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Abbreviations: CHO, chinese hamster ovary; Ena, enabled; F-actin, filamentous actin; FMRP, fragile X mental retardation protein; kDa, kilodalton; LTP/LTD, long-term potentiation/long-term depression; Mena, mammalian enabled; NMDA, N-methyl-D-aspartate; N-WASP, neural Wiskott-Aldrich syndrome protein; SMN, survival of motor neuron protein; p42POP, p42 partner of profilin; PIP2, phosphatidylinositide-4,5-bisphosphate; VASP, vasodilator-stimulated phosphoprotein; WAVE, WASP-family verprolin homologue.

Table 1. Summary of Profilin genes in mammals and their proposed functions. Cell culture data performed with profilins from different sources have shown that profilins from different organisms and organs behave similarly with respect to actin cytoskeleton regulation, but some gene family member-specific interactions in neurons could explain the particular phenotype of profilin II deficiency in mice. See text for discussion of functions and additional references

Gene /Protein	Tissue distribution	General function	Neuronal function
Profilin I	Ubiquitously in nonmuscle cells[53]	– Regulation of the actin cytoskeleton – Essential for early development due to role in cell division[83] – Interaction with regulators of the endocytotic pathway[53] – nuclear export of actin[64], other putative nuclear functions[62]	Potential role in actin regulation during neuronal differentiation and plasticity processes[42,85]
Profilin II	Mainly in central nervous system[83]	– Similar to profilin I according to cell culture data – interaction with additional ligands via poly-L-proline binding site, especially ligands involved in vesicle trafficking [53]	Regulation of presynaptic plasticity processes; knockout data show potential role at the postsynapse and during differentiation can be carried out by profilin I[84]
Profilin III	Testis[3]	Unknown	—
Profilin IV	Testis[4]	Unknown	—

signalling cascade.[21] On the other hand, profilin binding to PIP2 precludes complex formation with actin due to overlapping binding sites and is a potential mechanism for extracellular signal-induced actin cytoskeleton rearrangement.[22] Furthermore profilin contains a polyproline-binding motif[23] (cf. Fig. 1), making it eligible for binding to a variety of binding partners referred to as profilin ligands (reviewed in Refs 24,25). Although binding to these partners could imply regulation of

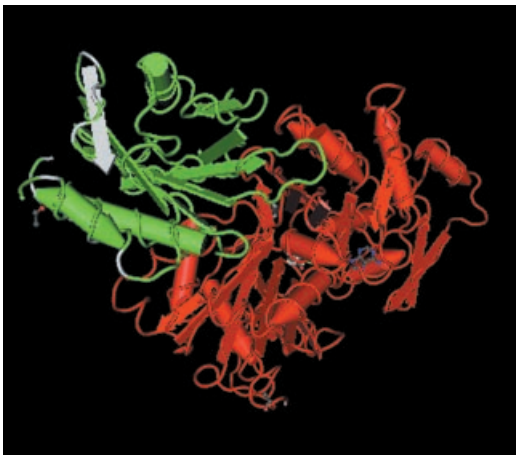

Figure 1. Three-dimensional structure of bovine profilin I bound to β-actin based on resolution by X-ray crystallography.[92] Profilin (green) binds to actin (red) using a binding domain distinct from the poly-L-proline binding domain, which is responsible for interaction with other profilin protein ligands. Residues necessary for poly-L-proline binding are depicted in white (left). This figure was generated using NCBI Cn3D software and NCBI structure file 2BTF.

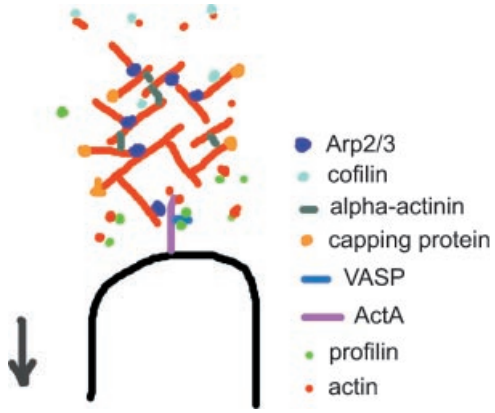

Figure 2. An in vitro assay for actin-based motility. Certain pathogens traverse the cytoplasm of host cells such as gut epithelial cells by exploiting the host cell's actin assembling machinery. Their secret is the localized expression of proteins such as Listeria monocytogene's ActA, which bind to host proteins regulating actin assembly, such as the Arp2/3 complex or VASP (reviewed in Ref. 93). The net result depending on a number of actin-regulating proteins is an actin "comet tail" propelling the bacterium through the cell (net movement indicated by the arrow in Fig. 2). This movement can be reconstituted in vitro using purified proteins and either the bacterium or the bacterial protein coupled to an inorganic bead.[94] For Listeria, Arp2/3, cofilin and capping protein are required for in vitro motility, while the inclusion of alpha-actinin, VASP and low concentrations of profilin enhances the movement.[14] This is in line with the proposed role for profilin in adding actin monomers to the growing end of the actin filament.

the actin cytoskeleton at complexes or microdomains containing profilin ligands, actin-independent roles for profilin are possible. In various cell lines, profilin interacting with actin accounts for only 20% of the total profilin pool.[26] The great abundance of profiling-binding sites could potentially attract profilin concentrations in the millimolar range in specialized microdomains.[17] Therefore local changes in profilin concentration can play a role in modulation of the actin cytoskeleton as well as in signal transduction cascades involved in a variety of cellular processes.

In this review, I want to focus on profilin's role in neuronal cells, its regulation of the actin cytoskeleton at different levels of neuronal differentiation and in the mature neuron. Profilin functions as a regulator of both pre- and postsynaptic mechanisms, via actin-dependent and potentially actin-independent mechanisms. Localization changes during neuronal activity combined with recent data from mouse models and neuronal diseases identify profilin as an important factor in both cellular and behavioural plasticity.

Profilin and actin dynamics

Too much of a good thing

Actin-based motility in mammalian cells occurs at specialized domains, wave-like protrusions called lamellipodia and membrane ruffles from which often emerge spike-like protrusions called filopodia.[27] The net result of motility in these microdomains is based on a highly regulated process involving rearrangements of actin organizations and depends on a plethora of actin-regulating proteins.[28] Profilin holds a special role in this process as it is one of the most-promiscuous proteins in this setting. It binds not only directly to actin, but also to regulating proteins such as Enabled/mammalian enabled/vasodilator-stimulated phosphoprotein (Ena/Mena/VASP) family members, neural Wiskott-Aldrich syndrome protein (N-WASP), mDiaphanous, other actin-binding proteins like drebrin, and directly to lipids such as PIP2.[20,29–32] Current models of motility emphasize the need for control of protein levels to funnel activity, as exemplified in a model for directed motility dependent on a capping of actin polymers, leaving free a few selected polymer strands which will grow.[33,34] Thus it is conceivable that overexpression or depletion of certain proteins within a microdomain can interfere with directed motility. Consistent with this hypothesis, profilin has been shown to strongly inhibit the formation of lamellipodia when microinjected into rat kidney cells.[35] Also, stable genetic overexpression of profilin in Chinese hamster ovary (CHO) cells stabilized dynamic actin structures.[15] However, one difference between these two studies is the decrease in filamentous actin (F-actin) in the former in contrast to an increase of F-actin in the latter study. This difference emphasizes the need to observe the relative changes in many actin-regulating proteins in order to understand filament formation and degradation. For example, in vitro experiments revealed that profilin can maintain actin levels steadily in the presence of capping proteins, while causing a loss in filaments in their absence.[36] However, the stabilization of dynamic structures caused by a local overabundance of profilin is a general theme also evident in other in vivo situations. Thus, overexpression of profilin reduces the migration of invasive breast cancer cells[37] and strong ectopic expression of profilin I increases adhesion of endothelial cells to certain extracellular matrices.[38] Consistent with this, profilin I containing a functional actin-binding site can function as a tumour suppressor.[39,40]

Implications for the neuronal cytoskeleton

In neurons, these decreased dynamics caused by high local profilin levels go hand in hand with increased stability of the actin network at different levels of neuronal differentiation. In the early phase of establishing a neuronal phenotype, the neuronal sphere is broken by a local instability of actin at the cell cortex, giving rise to the formation of lamellipodia and filopodia.[41] Neuronal profilin II is a regulator of cortical actin, and profilin overexpression leads to suppression of neuritogenesis, while downregulation increases the number of neurites formed[42] (Fig. 3a,b). This stabilizing role of profilin is mediated by RhoA, a member of the Ras superfamily of small GTPases, and the subsequent activation of the protein kinase Rho kinase (ROCK). These results have also been confirmed for profilin I in PC12 cells, a non-neuronal model system for neurite outgrowth.[43] The regulatory role of profilin in the cortical actin cytoskeleton of the neuronal sphere are likely modulated by Ena/VASP proteins, which themselves are necessary for neuritogenesis.[44,45]

In mature large pyramidal neurons of the cortex and hippocampus, among others, high actin concentrations are found at postsynaptic dendritic spines.[46] The highly dynamic actin cytoskeleton gives rise to morphological dynamics of dendritic spines resembling lamellipodia-like protrusions in other cell types.[47] Brain-specific profilin II has been found to be an essential element for stabilization of this morphological plasticity[48] (Fig. 3c,d). Moreover, blocking interaction of profilin with polyproline-rich regulators in the spine increases the morphological dynamics and impairs stabilization by neurotransmitter flux from the presynapse.

Profilin could have a similar stabilizing function in neuronal growth cone filopodia, where equivalent preconditions for activity-induced targeting are present. Hence, a polyproline-rich profilin ligand, Mena, localizes to the tips of growth cones,[49] and activity-induced stabilization of the actin cytoskeleton is analogous in growth cone filopodia and spines[50,51] (Fig. 3e,f). Axons from Mena-deficient mice are misrouted, and Mena deficiency plus profilin I heterozygosity leads to defects in neurulation.[49] Profilin deficiency also

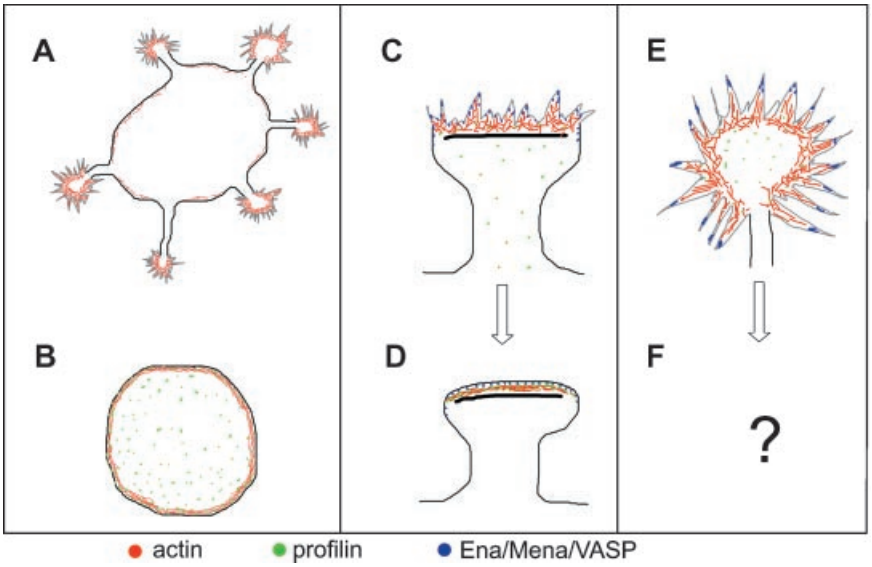

Figure 3. High profilin expression induces stabilization of the cortical actin cytoskeleton in different neuronal actin-rich structures. **A:** In the normally developing neuron, the neuronal sphere is broken by protruding neurites at sites of local actin instability, leading to neuritogenesis. The motile elements (grey), i.e. growth cones, at the tips of neurites show a dynamic actin cytoskeleton (red) based on the interplay of many actin-regulating molecules including profilin (green). **B:** Overexpression of profilin leads to stabilization of the cortical actin cytoskeleton, preventing neuritogenesis. **C:** The actin cytoskeleton at the tips of postsynaptic dendritic spines shows a high degree of motility (grey), dependent on a dynamic actin cytoskeleton (red). **D:** Upon stimulation of postsynaptic NMDA receptors and calcium influx, profilin (green) targets to spine heads, a movement likely dependent on membrane-associated molecules of the Ena/Mena/VASP family (blue; see text). Profilin is one essential factor in the stabilization of spine morphology, leading to rounding of the spine head and a halt in morphological plasticity. **E:** In neuronal growth cones, the peripheral zone consists of a highly motile combination of lamellipodia and protruding filopodia, and Mena (blue) has been shown to localize to the tips of filopodia. **F:** Although profilin mutants show phenotypes suggesting defects in growth cone guidance and profiling, ligands are present in the growth cone (see above), experiments testing the exact role of profilin in growth cone turning or collapse have not been published.

leads to premature arrest of axons during pathfinding in Drosophila.[52]

Taken together, these results implicate profilin as an important regulator of the neuronal cytoskeleton during differentiation and plasticity processes (Fig. 3).

Membrane trafficking and functions along the secretory pathway

Profilins interact with a wide variety of proteins via their poly-L-proline binding site, and interestingly profilin I and II differ in their binding affinities for poly-L-proline. A screen in mouse brain for profilin ligands revealed that a number of profilin-interacting molecules are part of the secretory machinery.[53] This is in agreement with genetic data from yeast and Drosophila identifying profilin as a necessary element in membrane trafficking and endocytosis.[54,55] In mouse brain, the interaction between profilin II and the GTPase dynamin I was characterized in more detail.[56] Dynamin I is a central regulator of endocytosis specific to neurons and thought to regulate the membrane fission process of budding vesicles. Together with its effector molecules like endophilin and ampiphysin, dynamin has been shown to localize presynaptically.[57,58] Profilin II overexpression inhibits endocytosis by sequestering dynamin binding sites from downstream effector molecules. This interaction between profilin and dynamin is regulated by PIP2, and thus one can speculate about a common regulation of endocytosis and actin polymerization at phosphatidylinositol-rich membranes.

The protein Citron-N, required for functional integrity of the Golgi apparatus in neurons, interacts with an actin-regulating complex involving profilin II in hippocampal neurons.[59] Profilin II downregulation destabilizes Golgi architecture by weakening the actin cytoskeleton at the Golgi cisternae. Strikingly, Citron-N has also been shown to localize to postsynaptic sites.[60,61] Furthermore, profilin interactions with other proteins of the neuronal endocytotic machinery such as clathrin or synapsin have not been characterized functionally and may still deliver further insights into the role of profilin in membrane trafficking.

Nuclear profilin

Profilin has been suspected to be present in the nucleus for a long time. Given its small size and globular tertiary structure, it should in fact be able to passively diffuse through the nuclear

pore when not bound to interaction partners in the cytoplasm. Detailed immunolocalization studies in fibroblasts using different specific antibodies demonstrated that the ubiquitous protein profilin I colocalizes with nuclear subcompartments, splicing speckles and Cajal bodies.[62] In accordance with this localization, function-blocking antibodies against profilin inhibited splicing in an in vitro assay. Similar to other recently discovered profilin functions, it is currently unknown whether a putative role in splicing is carried out independent of actin, although other actin-binding proteins have been implicated in regulation of splicing.[63]

In regular interphase cells, profilin entering the nucleus is exported together with actin by means of a specific export receptor, exportin 6.[64] The existence of a nuclear transport system specific for profilin and actin suggests that tight regulation of nuclear profilin and actin levels is important and that modulation of this export pathway specifically influences nuclear functions of these proteins. Of note, Drosophila profilin has been shown to be necessary for general nuclear export in genetic complementation assays.[65]

Concerning a possible function for nuclear profilin, the interaction between profilin and SMN (survival of motorneuron protein) indicates a putative role in RNA processing.[66] More recently a novel transcriptional modulator termed p42POP (partner of profilin) highly expressed in brain was identified.[67] This protein not only interacts with profilin in the nucleus, but its activity is influenced by profilin binding. This suggests a role for profilin in regulating neuronal transcription.

In conclusion, current data lead to the hypothesis that passive nuclear import and tightly regulated nuclear export control a nuclear function for profilin in neuronal gene expression.

Profilin and neuronal plasticity

Actin-based plasticity at postsynaptic dendritic spines, the most-abundant postsynaptic structure at excitatory synapses in the mammalian brain, is considered to be an anatomical correlate to electrophysiological changes of synaptic plasticity.[68] Particularly, long-term potentiation (LTP), regarded as the neural correlate of learning and memory, has been shown to depend on a dynamic actin cytoskeleton.[69,70] Profilin was the first actin-binding protein to be identified to redistribute to postsynaptic sites upon stimulation of postsynaptic N-methyl-D-aspartate (NMDA) receptors and influx of extracellular calcium, which is the signalling pathway leading to LTP.[48] Profilin was shown to be a necessary element in the following activity-dependent stabilization of dendritic spine morphology, which is irreversible for at least several hours, further underlining analogies to long-term electrophysiological plasticity. Importantly, activity-induced profilin targeting to synapses has been demonstrated in vivo in the fear-conditioning paradigm of amygdala-dependent learning.[71] Fear conditioning of rats drives profilin into dendritic spines, which is associated with lengthening of postsynaptic densities, an important factor in synaptic plasticity.

Moreover, NMDA receptor activation and calcium influx also lead to nuclear accumulation of profilin by a mechanism involving actin accumulation at the cell cortex.[72] Consequently profilin cannot be exported from the nucleus by the actin/profilin interaction with exportin 6 and accumulates as long as NMDA receptors are stimulated, leading to an activity-dependent and reversible nuclear accumulation. This bidirectional redistribution of profilin upon synaptic activity may link synaptic plasticity to gene expression. Long-term memory and synaptic plasticity have been shown to be dependent on translation and transcription.[73] A role for profilin in regulating these processes is suggested by its nuclear interaction partners like the transcriptional regulator p42POP.[67] Profilin thus matches properties of a ''synaptic tag''. Synaptic tagging refers to a proposed mechanism by which a mark is set at individual synapses while nuclear events necessary for long-term consolidation are initiated[74] (Fig. 4). According to this theory, macromolecules (RNA and proteins) expressed in response to neuronal activity are captured exclusively by synapses ''tagged'' by a molecule or molecular complex whose presence is induced by synaptic activity. The bidirectional targeting of profilin to synapses and the nucleus is in line with this proposal.

Additionally, further roles of neuronal profilin have been established, albeit their relationship to neuronal activity is still poorly defined. Interestingly, dynamin I, a major interaction partner for profilin II has been shown to be a central regulator of activity-stimulated synaptic vesicle recycling.[75] Thus profilin may be involved in both pre- and postsynaptic activity-dependent plasticity (Fig. 4). Furthermore, profilin is also found at the postsynapse of inhibitory synapses in a complex with the scaffolding molecule gephyrin and the microfilament adaptor Mena.[76]

Profilin malfunction in disease and animal models

As a molecule involved in plasticity processes at different levels, profilin might be expected to be involved in various neurological syndromes. In fact, one pathological situation characterized by striking abnormalities in dendritic spine morphology is Fragile X syndrome.[77,78] This disease is caused by loss of the fragile X syndrome protein (FMRP) which has been shown to function as an RNA-binding protein involved in local protein synthesis at synapses.[79] FMRP is highly conserved during evolution and the Drosophila homologue dFMRP was shown to bind profilin mRNA and regulate profilin protein levels.[80] Importantly, genetic complementation assays showed that phenotypes in the collateral branch formation of large ventrolateral cells and mushroom body formation could be explained by misregulation of profilin expression by dFMRP.

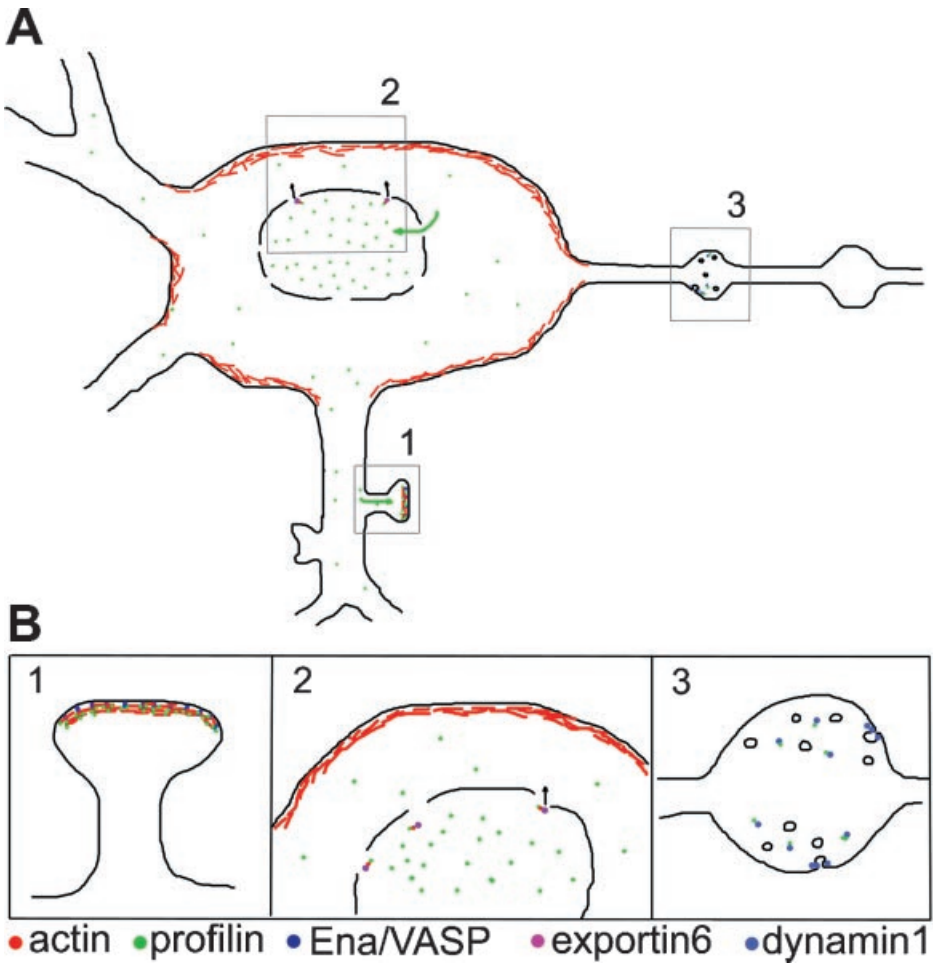

Figure 4. Strong neuronal activity leads to profilin redistribution in different neuronal compartments. **A:** Schematic view of a strongly depolarized neuron with postsynaptic sites (1), nuclear/cytoplasmic interface (2), and presynaptic axonal boutons (3). Profilin is involved in activity-dependent plasticity at these compartments. **B:** Boxes of compartments in A in a magnified view. **B1:** Synaptic activity leads to a strong redistribution of profilin from the dendritic shaft to spine heads, where polyproline-rich molecules of the Ena/Mena/VASP family (blue) are likely ligands, leading to stabilization of the actin cytoskeleton (red). **B2:** Strong NMDA receptor activation and subsequent influx of calcium ions leads to nuclear accumulation of profilin. This is likely due to the inability of actin to transport profilin out of the nucleus by its specific transporter molecule exportin 6 (pink), as monomeric actin is sequestered into filaments at the cell cortex. **B3:** Strong activity at the presynapse needs the GTPase dynamin I for efficient endocytosis. Dynamin I (purple) interacts with profilin II and its activity is regulated by this interaction, demonstrating another putative mode of action of profilin in activity-dependent plasticity.

Furthermore, profilin's interaction with the survival of motor neuron protein SMN implies a role in one of the many functions of SMN in RNA processing or transport. Downregulation of profilin leads to accumulation of SMN in cytoplasmic aggregates.[81] This indicates that spinal muscular atrophy, caused by a lack of functional SMN, may be phenotypically explained by the inability to exert profilin-dependent functions.

Profilin also interacts with huntingtin, the protein mutated in Huntington's disease. Mutant huntingtin leads to downregulation of profilin protein levels and the disease phenotype can be restored by ectopic profilin expression in a Drosophila eye model.[82]

Finally, profilin-deficient mice have been created, and knockout of the ubiquitously expressed profilin I results in embryonic lethality as early as the 2-cell stage due to defects in cytokinesis.[83] The development of profilin II-deficient mice has recently been reported, with mice being hyperactive and showing increased novelty-seeking behaviour.[84] This is correlated with hyper-excitability and higher vesicle release probability in knockout neurons. Molecularly, the phenotype may be explained by an isoform-specific interaction of profilin II with the WASP-family verprolin homologue (WAVE)-complex, leading to impaired presynaptic actin polymerization. Surprisingly, long-term potentiation and depression (LTP/LTD) and

learning are normal in profilin II$^{-/-}$ mice. Further studies on animals and neurons lacking both profilin I and II in the brain will help to elucidate gene family member-specific and redundant functions, as profilin I has, for example, been shown to undergo a similar activity-dependent postsynaptic targeting as profilin II.[85]

Conclusion and outlook

In conclusion, profilin plays a role in various processes of neuronal plasticity during development and in the adult. In the past, much emphasis has been laid on profilin's regulatory role of the actin cytoskeleton in neuronal differentiation. In fact, cytoskeletal dynamics in dendritic spines lie at the heart of synaptic plasticity and deregulation of the actin cytoskeleton alone probably has a profound impact on higher brain functions. Long-term potentiation and depression are associated with actin-dependent growth and shrinkage of the postsynaptic spine, respectively.[86] Both LTP- and LTD-inducing stimuli lead to stabilization of actin dynamics through profilin recruitment.[48] The difference in morphological change is likely mediated by a well-regulated interplay of several actin-binding proteins. For instance, the activity-regulated cytoskeleton-associated protein Arc is required for the expression of LTP and generation of stably modified synapses concomitant with dephosphorylation of cofilin.[87] In recent years a number of actin-regulatory proteins have been identified involved in pre-and postsynaptic plasticity (reviewed in Ref. 88). However, profilin seems to be an important regulator of plasticity processes beyond the cytoskeleton and may offer means to influence neuronal function at different levels. It thus embodies qualities of neuronal plasticity as a whole, representing processes that change constituents of neuronal circuits on the short and long term.

Further work in the field will elucidate the contributions of individual profilin family members to its distinct functions. As profilin II-deficient mice have shown, presynaptic roles of profilin are mainly carried out by this protein, while roles in neuronal differentiation and activity-dependent postsynaptic stabilization could be adopted by profilin I. Further animal models, such as brain-specific deletions of all profilins or cellular domain-specific interference with profilin function in vivo will give further insight into profilin function at different levels of neuronal plasticity. Some intriguing profilin interactions such as those with presynaptic matrix proteins aczonin/Piccolo[89] and vesicle proteins clathrin or synapsin will be characterized in more detail and provide us with a better understanding of the molecular machinery during activity-dependent vesicle release. Finally, the prospect of nuclear profilin, its interaction with potential transcriptional regulators and the exciting discoveries of nuclear actin as a regulator of chromatin-positioning of transcriptionally active genes[90,91] lay the foundation for future experiments towards understanding this aspect of long-term changes in neuronal connectivity through changes in gene expression.

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References

1. Carlsson L, Nystrom LE, Sundkvist I, Markey F, Lindberg U. 1977. Actin polymerizability is influenced by profilin, a low molecular weight protein in non-muscle cells. J Mol Biol 115:465–483.
2. Honore B, Madsen P, Andersen AH, Leffers H. 1993. Cloning and expression of a novel human profilin variant, profilin II. FEBS Lett 330: 151–155.
3. Hu E, Chen Z, Fredrickson T, Zhu Y. 2001. Molecular cloning and characterization of profilin-3: a novel cytoskeleton-associated gene expressed in rat kidney and testes. Exp Nephrol 9:265–274.
4. Obermann H, Raabe I, Balvers M, Brunswig B, Schulze W, et al. 2005. Novel testis-expressed profilin IV associated with acrosome biogenesis and spermatid elongation. Mol Hum Reprod 11:53–64.
5. Polet D, Lambrechts A, Vandepoele K, Vandekerckhove J, Ampe C. 2007. On the origin and evolution of vertebrate and viral profilins. FEBS Lett 581:211–217.
6. Rothkegel M, Mayboroda O, Rohde M, Wucherpfennig C, Valenta R, et al. 1996. Plant and animal profilins are functionally equivalent and stabilize microfilaments in living animal cells. J Cell Sci 109:83–90.
7. Nodelman IM, Bowman GD, Lindberg U, Schutt CE. 1999. X-ray structure determination of human profilin II: A comparative structural analysis of human profilins. J Mol Biol 294:1271–1285.
8. DiNubile MJ, Southwick FS. 1985. Effects of macrophage profilin on actin in the presence and absence of acumentin and gelsolin. J Biol Chem 260:7402–7409.
9. Mockrin SC, Korn ED. 1980. Acanthamoeba profilin interacts with G-actin to increase the rate of exchange of actin-bound adenosine 5′-triphosphate. Biochemistry 19:5359–5362.
10. Tilney LG, Bonder EM, Coluccio LM, Mooseker MS. 1983. Actin from Thyone sperm assembles on only one end of an actin filament: a behavior regulated by profilin. J Cell Biol 97:112–124.
11. Pring M, Weber A, Bubb MR. 1992. Profilin-actin complexes directly elongate actin filaments at the barbed end. Biochemistry 31:1827–1836.
12. Pantaloni D, Carlier MF. 1993. How profilin promotes actin filament assembly in the presence of thymosin beta 4. Cell 75:1007–1014.
13. Southwick FS, Young CL. 1990. The actin released from profilin–actin complexes is insufficient to account for the increase in F-actin in chemoattractant-stimulated polymorphonuclear leukocytes. J Cell Biol 110:1965–1973.
14. Loisel TP, Boujemaa R, Pantaloni D, Carlier MF. 1999. Reconstitution of actin-based motility of Listeria and Shigella using pure proteins. Nature 401:613–616.
15. Finkel T, Theriot JA, Dise KR, Tomaselli GF, Goldschmidt-Clermont PJ. 1994. Dynamic actin structures stabilized by profilin. Proc Natl Acad Sci USA 91:1510–1514.
16. Syriani E, Gomez-Cabrero A, Bosch M, Moya A, Abad E, et al. 2008. Profilin induces lamellipodia by growth factor-independent mechanism. Faseb J 22:1581–1596.
17. Bubb MR, Yarmola EG, Gibson BG, Southwick FS. 2003. Depolymerization of actin filaments by profilin. Effects of profilin on capping protein function. J Biol Chem 278:24629–24635.
18. Sanger JM, Mittal B, Southwick FS, Sanger JW. 1995. Listeria monocytogenes intracellular migration: inhibition by profilin, vitamin D-binding protein and DNase I. Cell Motil Cytoskeleton 30:38–49.
19. Lassing I, Lindberg U. 1985. Specific interaction between phosphatidylinositol 4,5-bisphosphate and profilactin. Nature 314:472–474.

20. Lassing I, Lindberg U. 1988. Specificity of the interaction between phosphatidylinositol 4,5-bisphosphate and the profilin:actin complex. J Cell Biochem 37:255–267.
21. Goldschmidt-Clermont PJ, Machesky LM, Baldassare JJ, Pollard TD. 1990. The actin-binding protein profilin binds to PIP2 and inhibits its hydrolysis by phospholipase C. Science 247:1575–1578.
22. Goldschmidt-Clermont PJ, Kim JW, Machesky LM, Rhee SG, Pollard TD. 1991. Regulation of phospholipase C-gamma 1 by profilin and tyrosine phosphorylation. Science 251:1231–1233.
23. Tanaka M, Shibata H. 1985. Poly(L-proline)-binding proteins from chick embryos are a profilin and a profilactin. Eur J Biochem 151:291–297.
24. Witke W. 2004. The role of profilin complexes in cell motility and other cellular processes. Trends Cell Biol 14:461–469.
25. Jockusch BM, Murk K, Rothkegel M. 2007. The profile of profilins. Rev Physiol Biochem Pharmacol 159:131–149.
26. Babcock G, Rubenstein PA. 1993. Control of profilin and actin expression in muscle and nonmuscle cells. Cell Motil Cytoskeleton 24: 179–188.
27. Small JV, Stradal T, Vignal E, Rottner K. 2002. The lamellipodium: where motility begins. Trends Cell Biol 12:112–120.
28. Pollard TD, Borisy GG. 2003. Cellular motility driven by assembly and disassembly of actin filaments. Cell 112:453–465.
29. Krause M, Dent EW, Bear JE, Loureiro JJ, Gertler FB. 2003. Ena/VASP proteins: regulators of the actin cytoskeleton and cell migration. Annu Rev Cell Dev Biol 19:541–564.
30. Suetsugu S, Miki H, Takenawa T. 1998. The essential role of profilin in the assembly of actin for microspike formation. Embo J 17:6516–6526.
31. Watanabe N, Madaule P, Reid T, Ishizaki T, Watanabe G, et al. 1997. p140mDia, a mammalian homolog of Drosophila diaphanous, is a target protein for Rho small GTPase and is a ligand for profilin. Embo J 16:3044–3056.
32. Mammoto A, Sasaki T, Asakura T, Hotta I, Imamura H, et al. 1998. Interactions of drebrin and gephyrin with profilin. Biochem Biophys Res Commun 243:86–89.
33. Dufort PA, Lumsden CJ. 1996. How profilin/barbed-end synergy controls actin polymerization: a kinetic model of the ATP hydrolysis circuit. Cell Motil Cytoskeleton 35:309–330.
34. Carlier MF, Pantaloni D. 1997. Control of actin dynamics in cell motility. J Mol Biol 269:459–467.
35. Cao LG, Babcock GG, Rubenstein PA, Wang YL. 1992. Effects of profilin and profilactin on actin structure and function in living cells. J Cell Biol 117:1023–1029.
36. Helfer E, Nevalainen EM, Naumanen P, Romero S, Didry D, et al. 2006. Mammalian twinfilin sequesters ADP-G-actin and caps filament barbed ends: implications in motility. Embo J 25:1184–1195.
37. Roy P, Jacobson K. 2004. Overexpression of profilin reduces the migration of invasive breast cancer cells. Cell Motil Cytoskeleton 57:84–95.
38. Moldovan NI, Milliken EE, Irani K, Chen J, Sohn RH, et al. 1997. Regulation of endothelial cell adhesion by profilin. Curr Biol 7:24–30.
39. Janke J, Schluter K, Jandrig B, Theile M, Kolble K, et al. 2000. Suppression of tumorigenicity in breast cancer cells by the microfilament protein profilin 1. J Exp Med 191:1675–1686.
40. Wittenmayer N, Jandrig B, Rothkegel M, Schluter K, Arnold W, et al. 2004. Tumor suppressor activity of profilin requires a functional actin binding site. Mol Biol Cell 15:1600–1608.
41. da Silva JS, Dotti CG. 2002. Breaking the neuronal sphere: regulation of the actin cytoskeleton in neuritogenesis. Nat Rev Neurosci 3:694–704.
42. Da Silva JS, Medina M, Zuliani C, Di Nardo A, Witke W, et al. 2003. RhoA/ROCK regulation of neuritogenesis via profilin IIa-mediated control of actin stability. J Cell Biol 162:1267–1279.
43. Lambrechts A, Jonckheere V, Peleman C, Polet D, De Vos W, et al. 2006. Profilin-I-ligand interactions influence various aspects of neuronal differentiation. J Cell Sci 119:1570–1578.
44. Dent EW, Kwiatkowski AV, Mebane LM, Philippar U, Barzik M, et al. 2007. Filopodia are required for cortical neurite initiation. Nat Cell Biol 9:1347–1359.
45. Kwiatkowski AV, Rubinson DA, Dent EW, Edward van Veen J, Leslie JD, et al. 2007. Ena/VASP Is Required for neuritogenesis in the developing cortex. Neuron 56:441–455.
46. Matus A, Ackermann M, Pehling G, Byers HR, Fujiwara K. 1982. High actin concentrations in brain dendritic spines and postsynaptic densities. Proc Natl Acad Sci USA 79:7590–7594.
47. Fischer M, Kaech S, Knutti D, Matus A. 1998. Rapid actin-based plasticity in dendritic spines. Neuron 20:847–854.
48. Ackermann M, Matus A. 2003. Activity-induced targeting of profilin and stabilization of dendritic spine morphology. Nat Neurosci 6:1194–1200.
49. Lanier LM, Gates MA, Witke W, Menzies AS, Wehman AM, et al. 1999. Mena is required for neurulation and commissure formation. Neuron 22:313–325.
50. Chang S, De Camilli P. 2001. Glutamate regulates actin-based motility in axonal filopodia. Nat Neurosci 4:787–793.
51. Fischer M, Kaech S, Wagner U, Brinkhaus H, Matus A. 2000. Glutamate receptors regulate actin-based plasticity in dendritic spines. Nat Neurosci 3:887–894.
52. Wills Z, Marr L, Zinn K, Goodman CS, Van Vactor D. 1999. Profilin and the Abl tyrosine kinase are required for motor axon outgrowth in the Drosophila embryo. Neuron 22:291–299.
53. Witke W, Podtelejnikov AV, Di Nardo A, Sutherland JD, Gurniak CB, et al. 1998. In mouse brain profilin I and profilin II associate with regulators of the endocytic pathway and actin assembly. Embo J 17:967–976.
54. Wolven AK, Belmont LD, Mahoney NM, Almo SC, Drubin DG. 2000. In vivo importance of actin nucleotide exchange catalyzed by profilin. J Cell Biol 150:895–904.
55. Pearson AM, Baksa K, Ramet M, Protas M, McKee M, et al. 2003. Identification of cytoskeletal regulatory proteins required for efficient phagocytosis in Drosophila. Microbes Infect 5:815–824.
56. Gareus R, Di Nardo A, Rybin V, Witke W. 2006. Mouse profilin 2 regulates endocytosis and competes with SH3 ligand binding to dynamin 1. J Biol Chem 281:2803–2811.
57. Takei K, McPherson PS, Schmid SL, De Camilli P. 1995. Tubular membrane invaginations coated by dynamin rings are induced by GTP-gamma S in nerve terminals. Nature 374:186–190.
58. Schmidt A, Wolde M, Thiele C, Fest W, Kratzin H, et al. 1999. Endophilin I mediates synaptic vesicle formation by transfer of arachidonate to lysophosphatidic acid. Nature 401:133–141.
59. Camera P, da Silva JS, Griffiths G, Giuffrida MG, Ferrara L, et al. 2003. Citron-N is a neuronal Rho-associated protein involved in Golgi organization through actin cytoskeleton regulation. Nat Cell Biol 5: 1071–1078.
60. Zhang W, Vazquez L, Apperson M, Kennedy MB. 1999. Citron binds to PSD-95 at glutamatergic synapses on inhibitory neurons in the hippocampus. J Neurosci 19:96–108.
61. Zhang W, Benson DL. 2006. Targeting and clustering citron to synapses. Mol Cell Neurosci 31:26–36.
62. Skare P, Kreivi JP, Bergstrom A, Karlsson R. 2003. Profilin I colocalizes with speckles and Cajal bodies: a possible role in pre-mRNA splicing. Exp Cell Res 286:12–21.
63. Rando OJ, Zhao K, Crabtree GR. 2000. Searching for a function for nuclear actin. Trends Cell Biol 10:92–97.
64. Stuven T, Hartmann E, Gorlich D. 2003. Exportin 6: a novel nuclear export receptor that is specific for profilin.actin complexes. Embo J 22: 5928–5940.
65. Minakhina S, Myers R, Druzhinina M, Steward R. 2005. Crosstalk between the actin cytoskeleton and Ran-mediated nuclear transport. BMC Cell Biol 6:32.
66. Giesemann T, Rathke-Hartlieb S, Rothkegel M, Bartsch JW, Buchmeier S, et al. 1999. A role for polyproline motifs in the spinal muscular atrophy protein SMN. Profilins bind to and colocalize with smn in nuclear gems. J Biol Chem 274:37908–37914.
67. Lederer M, Jockusch BM, Rothkegel M. 2005. Profilin regulates the activity of p42POP, a novel Myb-related transcription factor. J Cell Sci 118:331–341.
68. Matus A. 2000. Actin-based plasticity in dendritic spines. Science 290: 754–758.
69. Kim CH, Lisman JE. 1999. A role of actin filament in synaptic transmission and long-term potentiation. J Neurosci 19:4314–4324.
70. Krucker T, Siggins GR, Halpain S. 2000. Dynamic actin filaments are required for stable long-term potentiation (LTP) in area CA1 of the hippocampus. Proc Natl Acad Sci USA 97:6856–6861.

71. Lamprecht R, Farb CR, Rodrigues SM, LeDoux JE. 2006. Fear conditioning drives profilin into amygdala dendritic spines. Nat Neurosci 9:481–483.
72. Birbach A, Verkuyl JM, Matus A. 2006. Reversible, activity-dependent targeting of profilin to neuronal nuclei. Exp Cell Res 312:2279–2287.
73. McGaugh JL. 2000. Memory—a century of consolidation. Science 287:248–251.
74. Frey U, Morris RG. 1998. Synaptic tagging: implications for late maintenance of hippocampal long-term potentiation. Trends Neurosci 21:181–188.
75. Ferguson SM, Brasnjo G, Hayashi M, Wolfel M, Collesi C, et al. 2007. A selective activity-dependent requirement for dynamin 1 in synaptic vesicle endocytosis. Science 316:570–574.
76. Giesemann T, Schwarz G, Nawrotzki R, Berhorster K, Rothkegel M, et al. 2003. Complex formation between the postsynaptic scaffolding protein gephyrin, profilin, and Mena: a possible link to the microfilament system. J Neurosci 23:8330–8339.
77. Hinton VJ, Brown WT, Wisniewski K, Rudelli RD. 1991. Analysis of neocortex in three males with the fragile X syndrome. Am J Med Genet 41:289–294.
78. Rudelli RD, Brown WT, Wisniewski K, Jenkins EC, Laure-Kamionowska M, et al. 1985. Adult fragile X syndrome. Clinico-neuropathologic findings. Acta Neuropathol (Berl) 67:289–295.
79. Garber K, Smith KT, Reines D, Warren ST. 2006. Transcription, translation and fragile X syndrome. Curr Opin Genet Dev 16:270–275.
80. Reeve SP, Bassetto L, Genova GK, Kleyner Y, Leyssen M, et al. 2005. The Drosophila fragile X mental retardation protein controls actin dynamics by directly regulating profilin in the brain. Curr Biol 15:1156–1163.
81. Sharma A, Lambrechts A, Hao le T, Le TT, Sewry CA, et al. 2005. A role for complexes of survival of motor neurons (SMN) protein with gemins and profilin in neurite-like cytoplasmic extensions of cultured nerve cells. Exp Cell Res 309:185–197.
82. Burnett BG, Andrews J, Ranganathan S, Fischbeck KH, Di Prospero NA. 2008. Expression of expanded polyglutamine targets profilin for degradation and alters actin dynamics. Neurobiol Dis 30:365–374.
83. Witke W, Sutherland JD, Sharpe A, Arai M, Kwiatkowski DJ. 2001. Profilin I is essential for cell survival and cell division in early mouse development. Proc Natl Acad Sci USA 98:3832–3836.
84. Pilo Boyl P, Di Nardo A, Mulle C, Sassoe-Pognetto M, Panzanelli P, et al. 2007. Profilin2 contributes to synaptic vesicle exocytosis, neuronal excitability, and novelty-seeking behavior. Embo J 26:2991–3002.
85. Neuhoff H, Sassoe-Pognetto M, Panzanelli P, Maas C, Witke W, et al. 2005. The actin-binding protein profilin I is localized at synaptic sites in an activity-regulated manner. Eur J Neurosci 21:15–25.
86. Okamoto K, Nagai T, Miyawaki A, Hayashi Y. 2004. Rapid and persistent modulation of actin dynamics regulates postsynaptic reorganization underlying bidirectional plasticity. Nat Neurosci 7:1104–1112.
87. Messaoudi E, Kanhema T, Soule J, Tiron A, Dagyte G, et al. 2007. Sustained Arc/Arg3.1 synthesis controls long-term potentiation consolidation through regulation of local actin polymerization in the dentate gyrus in vivo. J Neurosci 27:10445–10455.
88. Cingolani LA, Goda Y. 2008. Actin in action: the interplay between the actin cytoskeleton and synaptic efficacy. Nat Rev Neurosci 9:344–356.
89. Wang X, Kibschull M, Laue MM, Lichte B, Petrasch-Parwez E, et al. 1999. Aczonin, a 550-kD putative scaffolding protein of presynaptic active zones, shares homology regions with Rim and Bassoon and binds profilin. J Cell Biol 147:151–162.
90. Chuang CH, Carpenter AE, Fuchsova B, Johnson T, de Lanerolle P, et al. 2006. Long-range directional movement of an interphase chromosome site. Curr Biol 16:825–831.
91. Dundr M, Ospina JK, Sung MH, John S, Upender M, et al. 2007. Actin-dependent intranuclear repositioning of an active gene locus in vivo. J Cell Biol 179:1095–1103.
92. Schutt CE, Myslik JC, Rozycki MD, Goonesekere NC, Lindberg U. 1993. The structure of crystalline profilin-beta-actin. Nature 365:810–816.
93. Stevens JM, Galyov EE, Stevens MP. 2006. Actin-dependent movement of bacterial pathogens. Nat Rev Microbiol 4:91–101.
94. Cameron LA, Footer MJ, van Oudenaarden A, Theriot JA. 1999. Motility of ActA protein-coated microspheres driven by actin polymerization. Proc Natl Acad Sci USA 96:4908–4913.