Profilin—A master coordinator of actin and microtubule organization in mammalian cells

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Abstract
The last two decades have witnessed a tremendous increase in cell biology data. Not least is this true for studies of the dynamic organization of the microfilament and microtubule systems in animal cells where analyses of the molecular components and their interaction patterns have deepened our understanding of these complex force-generating machineries. Previous observations of a molecular cross-talk between the two systems have now led to the realization of the existence of several intricate mechanisms operating to maintain their coordinated cellular organization. In this short review, we relate to this development by discussing new results concerning the function of the actin regulator profilin 1 as a control component of microfilament-microtubule cross-talk.

KEYWORDS
actin microtubule cross-talk, cell migration, cytoarchitecture regulation, cytoskeletal control, profilin

INTRODUCTION
Clarence E. Schutt once stated that “there is no such a thing as a boring protein” (Schutt, 1985). Definitely, the actin regulator profilin is a good illustration of this statement.

Along with proteins such as ADF/cofilin, thymosin, and gelsolin, profilin (in the following “profilin” refers to profilin 1 unless otherwise is stated) is a classical interaction partner to nonmuscle actin (β- and γ-actin), and tightly associated with the control of actin polymerization (Carlsson et al., 1977; Pernier et al., 2016). Profilin was originally identified through the pioneering work by Lindberg (1967a, 1967b) who, upon the characterization of the DNase I inhibitor found that this protein component isolated from calf spleen consisted of nonmuscle actin (Lazarides & Lindberg, 1974) and a small protein (Carlsson et al., 1976) subsequently shown to control actin polymerization (Carlsson et al., 1977). On basis of its presumed function to keep actin “profilamentous” this component was named “profilin” (Carlsson et al., 1977) and the complex with actin “profilactin” after Tilney who had found a non-filamentous form of actin in the subacrosomal cup of Thyon sperm (Tilney, 1976). Since several years the complex is generally referred to as profilin-actin. See further Karlsson and Lindberg (2007) for a brief treatise of early profilin studies.

Subsequent studies unveiled the functional complexity of profilin as a regulator of actin polymerization. Evidently, it inhibits actin nucleation, but in the presence of filaments, it had little effect on filament elongation unless filament (+)-end blocking proteins were present, indicating that profilin somehow probed filament asymmetry (Markey et al., 1982; Pollard & Cooper, 1984; Tilney

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Both actin filaments and microtubules are asymmetric polymers characterized by a fast and slow polymerizing end, conventionally referred to as (+) and (−) ends, respectively. The solving of the profilin–β-actin structure (Schutt et al., 1993) established that profilin binds the actin monomer (G-actin) at a surface matching the site exposed at the filament (+)-end and therefore leaves profilin–actin with a free actin surface to interact with unblocked filament (+)-ends. This allows for practically non-compromised filament elongation despite profilin’s actin sequestering capacity; only if the (+)-end is blocked does sequestering by profilin interfere with filament growth. This ability of profilin is of key-importance for its control of actin. Another important feature is that it efficiently enhances the exchange of the actin-bound nucleotide and thereby facilitates the replacement of ADP for ATP (Korenbaum et al., 1998; Mockrin & Korn, 1980). Since profilin inhibits the actin ATPase (Nyman et al., 2002; Tobacman & Korn, 1982), the consequence is that actin subunits added to the filament (+)-ends from profilin–actin carry ATP. Since actinATP is preferred over actinADP for incorporation at filament (+)-ends this means that profilin turns actin monomers into a polymerization-ready state.

**FIGURE 1** The backbone of the profilin molecule, displaying a summary of its major interaction surfaces and their linked activities. In the center, the open structure of profilin–β-actin is depicted (1HLU; Chik et al., 1996). Proflin (yellow backbone) contacts the “barbed side” of actin (light blue) at subdomains I and III. The highlighted profilin–actin contact H119-M355 is central for initiating the process, causing actin to attain an “open” conformation, accelerate actin nucleotide exchange and the loading of the actin monomer with ATP (see Baek et al., 2008; Chik et al., 1996; Porta & Borgstahl, 2012) for details. For clarity only one additional contact is highlighted K90-D286; for a complete description of interactions, see Schutt et al. (1993). The actin subdomains are denoted by Roman numerals (I–IV) and the backbone of the profilin N- and C-terminal helices appear in red. Packed at one side of the molecule they form an important regulatory region, see Panels a–c and text. Residue numbers follow established conventions with profilin starting with Ala1 (A1) and nonmuscle β-actin with Asp2 (D2), atom colors of highlighted residues are standard CPK-colors. The illustration was generated using MolSoft BrowserPro. Panel (a) poly(l-proline) binding. Four aromatic residues in the N- and C-terminal helices of profilin cluster to form the core of the poly(l-proline)-interacting surface. The position of the N-terminal helix is stabilized by W31 (not shown). This surface enables interaction with a range of actin nucleation and elongation promoting factors that carries the canonical GPβ-motif (see further Björkegren et al., 1993; Dickinson et al., 2002; Ferron et al., 2007; Mahoney et al., 1997; Mahoney et al., 1999). Note that actin-binding is nonperturbed by proteins associated with this surface. Panel (b) phosphatidylinositol lipid binding. The two regions of the profilin molecule depicted here have been identified as interacting with phosphatidylinositol lipids (Lambrechts et al., 2002; Skare & Karlsson, 2002). One region, involving residues A1, R135, R136 superimposes with the poly(l-proline)-binding surface while the other, consisting of K69, R88, K90 is engaged in actin subdomain III bindings. Residue K125 takes a critical position in this context. It forms a salt-bridge with E364 in actin subdomain I (Schutt et al., 1993), and is located in the nearness of the poly(l-proline)-binding surface. Possibly this residue contributes to electrostatic contacts that direct the lipid towards the actin surface, which ultimately leads to dissociation of the complex (see Skare & Karlsson, 2002) for further discussion. The highlighted residue H119 serves as a reference to the profilin–actin complex shown in the center. Panel (c) residues targeted by phosphorylation. Residues S137 and Y139 at the poly(l-proline)-binding surface (Björkegren-Sjögren, 1997; De Corte et al., 1997; Hansson et al., 1988) and Y128 (Fan et al., 2012) close to both the actin and poly(l-proline)-binding surfaces all have been observed to undergo phosphorylation under different conditions. The modification of Y128 was linked to angiogenesis, while the S137 phosphorylation is known to interfere with profilin’s binding to poly(l-proline) sequences (e.g., Gau et al., 2019; Shao et al., 2008). Panel d. Tubulin binding. The position of two residues M113 and G117 proposed to contribute to interaction with microtubules (Henty-Ridilla et al., 2017) is shown.
The profilin molecule folds into a one-domain structure built by a core of a seven-stranded, anti-parallel β-pleated sheets framed on one side by the α-helical N- and C-termini and on the other by two shorter α-helices (Cedergren-Zeppezauer et al., 1994; Schutt et al., 1993; see Figure 1). The packing of the N- and C-terminal helices forms the poly-β-proline (PLP)-binding surface (Björkegren-Sjögren et al., 1997; Björkegren et al., 1993; Mahoney et al., 1997). This site is of utmost functional significance for profilin’s role as a regulator of actin turnover; it enables profilin to simultaneously bind actin and many of the actin nucleation and elongation promoting factors (NEPFs) that carry PLP-sequences. Hence, proteins such as formins, Ena/VASP, WASP, and WAVE family members can recruit profilin:actin through this interaction to jointly operate to mediate actin polymerization at sites where filament formation is called for. This forms an efficient elongation machinery as illustrated by several observations both in vitro and in vivo (e.g., Breitsprecher et al., 2012; Funk et al., 2019; Hansen & Mullins, 2010; Higashida et al., 2004; Purich, 2016). Profilin also binds phosphatidylinositol lipids (PIP, PIP2, and PIP3) in an interaction that dissociates the profilin-actin complex (Lassing & Lindberg, 1985). This lipid-binding occurs at two surface regions of the molecule of which one partly overlaps with the PLP-binding surface (Lambrechts et al., 2002; Skare & Karlsson, 2002), pointing to this region as an important signaling hub within the molecule where different signaling pathways merge to indirectly control actin dynamics, see Figure 1. This area also harbors one or more target sites for phosphorylation (Björkegren-Sjögren, 1997; Diamond et al., 2015; Gau et al., 2019; Rizwani et al., 2014; Shao et al., 2008).

2 | THE MAMMALIAN PROFILIN FAMILY

Profilin 1 is ubiquitous and with a few exceptions the most abundant profilin variant present in vertebrate cells (Karlsson & Lindberg, 2007; Witke, 2004). The other members of the family, profilin 2a and 2b (splice variants of the same gene, Di Nardo et al., 2000)), and profilin 3 and 4 are less abundant. Due to being most richly occurring in the central nervous system, profilin 2 was originally coined “brain profilin”, however today it is realized that this profilin variant also is present in many other cell types (Funk et al., 2019; Joy et al., 2017; Mouneimne et al., 2012; Pimm et al., 2020), making this term misleading. The expression of profilin 3 and 4 is restricted to testis tissue (Behnen et al., 2008; Nodelman et al., 1999). Profilin 2b and 4 uniquely display a strongly reduced affinity for actin. From an evolutionary perspective, profilin 4 is considered to be closer to nonvertebrate profilins than the other ones (Polet et al., 2007).

3 | PROFILIN AS A REGULATOR OF ACTIN TURNOVER

As mentioned the original view of profilin as primarily an actin sequestering protein, which was concluded for instance after stimulation of platelets where an extensive actin polymerization (Karlsson et al., 1984) from profilin-actin was demonstrated (Blikstad et al., 1978; Markey et al., 1981) gradually changed with new insights of its functions. The facts that profilin accelerated actin nucleotide exchange and in association with actin, that is, as profilin-actin could dock with free filament (+)-ends became particularly important when it was realized that profilin could capture actin from the actin sequestering protein thymosin β4 and as profilin–actin hence make this pool of monomeric actin available for filament elongation (Pantalone & Carlier, 1993). Consequently, profilin could both sequester actin, that is, inhibit its nucleation and contribute to actin filament growth—a regulatory feat pending the dynamic molecular context of the situation. With the plethora of actin regulatory components characterized this view of profilin further matured and now it is widely accepted that profilin has a key-role coordinating the different sub-arrangements of actin along with other actin regulatory proteins such as cofilin, gelsolin, the Arp2/3-dependent NEPFs, formins, and Ena/Vasp that typically characterize the dynamic actin cytoarchitecture of most cells (Carlier & Shekhar, 2017; Henty-Ridilla & Goode, 2015; Mullins et al., 2018; Pernier et al., 2016; Rotty et al., 2015; Suarez & Kovar, 2016).

The location of profilin at the cell edge, close to the inner leaflet of the plasma membrane is well established, and although the steady-state ratio of profilin–actin to free profilin is unclear, the presence of profilin–actin is likely to be significant in this region given the central role of the profilin–actin complex as a source of polymerization competent actin. In support of this conjecture, profilin has been found to be crucial for the formation of cell protrusions such as lamellipodia and filopodia typically seen at advancing cell edges (Faust et al., 2019; Skruber et al., 2020). Moreover, reduced or completely blocked profilin expression strongly suppresses cell migration (Mouneimne et al., 2012; Nejedla et al., 2017). Hence, its juxtamembrane location, connection to signaling cues such as phosphatidylinositol lipid turnover (Lindberg et al., 2008), and actin polymerization during protrusion formation and cell migration indicate a crucial role of profilin for spatiotemporal control of cell edge processes and directional cell migration. This is further emphasized by the fact that tumor cells often show altered profilin expression along with changed morphologies and motile properties (Lindberg et al., 2008; Pimm et al., 2020).

4 | PROFILIN 1 AND MICROTUBULE ORGANIZATION

Several decades ago cell biologists while studying cultured rat fibroblasts after disruption of their actin and microtubule organizations made observations that led them to propose a functional
connection between these two fiber systems with actin being the force generator and microtubules controlling the directionality of movement (Vasiliev et al., 1970). This was way before the detailed characterization of the cytoskeleton as we know it today with the range of molecules identified to inflict on the dynamics of the systems and their coordinated organization and function, reviewed by Akhmanova and Steinmetz (2019), Dogterom and Koenderink, (2019), Meiring et al. (2020), and Seetharaman and Etienne-Manneville (2020).

An early indication of profilin being connected with microtubules was established by passing a mice brain extract through a column with immobilized profilin whereby tubulin was found among the captured proteins (Witke et al., 1998). Later immunofluorescence microscopy using different sets of affinity-purified antibodies generated against profilin-actin and purified against immobilized actin and profilin, respectively (Grenklo et al., 2004) showed partial co-distribution with microtubules in human skin fibroblasts. A subsequent report that profilin mRNA required an intact microtubule system to be properly distributed (Johnson & Karlsson, 2010) further suggested a connection that could be related to microtubule-dependent transportation similar to what had been observed for mRNAs encoding other actin-binding proteins (Mingle et al., 2005).

However, it was not until 2016 that the existence of a microtubule-profilin connection was demonstrated (Nejedlá et al., 2016). This paper convincingly presented data of profilin indirectly associating with microtubules most likely via formins and related mutations characterized previously (Wu et al., 2012). Current studies in this area are now focused to unravel the role for centrosome-related control of microfilament organization downstream of various cues. Previously, actin itself and several actin regulatory proteins were localized to the centrosome by different techniques including immunofluorescence microscopy and various mass spectroscopy approaches (Hubert et al., 2011; Jakobsen et al., 2011; Sabino et al., 2015). In some studies also the presence of focal adhesion-associated proteins was indicated (Fielding, Dobreva, & Dedhar, 2008; Fielding, Dobreva, McDonald, et al., 2008; Jakobsen et al., 2011; Pugacheva & Golemis, 2005, 2006). Interestingly enough, in the context of microfilament connections, also the GIT-PIX-PAK1 signaling cassette, which is involved in the regulation of actin rearrangements (Frank & Hansen, 2008) was found to be an important regulatory component of centrosomes (Zhao et al., 2005) where it was observed to control microtubule nucleation (Černohorská et al., 2016; Sulimenko et al., 2015). Therefore, it is likely that this signaling cassette plays a role for centrosome-proximal actin microfilament organization as well in analogy with other subcellular regions where also profilin operates as a key actin regulator (e.g., Faust et al., 2019; Skruber et al., 2020).

Later studies have furthered observations of centrosome-associated Arp2/3 (Hubert et al., 2011), the heptameric (Robinson et al., 2001) complex which operates jointly with WASP-family proteins to nucleate actin polymerization (Goley & Welch, 2006). The Arp2/3-complex was found to be associated with centrosome-derived filament formation (Farina et al., 2016; Obino et al., 2016) where it functioned with the WASP-related protein WASH as a nucleation-promoting factor (Farina et al., 2016). Furthermore, it has been shown that centrosomal actin nucleation is required for proper mitotic spindle formation (Plessner et al., 2019) and that regulation of centrosomal actin nucleation tunes the levels of centrosomal microtubules during mitotic exit (Farina et al., 2019). Of particular interest in the context of profilin are observations that microtubule growth apparently can be blocked by centrosomal actin filaments due to space constraints (Colin et al., 2018; Inoue et al., 2019).

The centrosome-related control of microfilament formation ought in our view to be considered in the perspective of advancing cell edge protrusions and directionality of cell migration, situations
which have been proposed to be centrosome-dependent in addition to the timing and orientation of the mitotic axis during cell division. Naturally, controlled coordination of actin and microtubule organization and their function during directional migration appears necessary for optimal cell behavior. This is underscored by the fact that stimulation of migration not only increases the formation of actin-dependent protrusions at the advancing lamellipod but also augments nucleation and extension of microtubules towards the leading edge (Meiring et al., 2020). Interestingly filamentous actin has been observed in the lumen of microtubules in extending projections induced by kinesin-1 (Paul et al., 2020). Although the significance of this observation with respect to centrosomal microtubule nucleation currently is unclear, the observation points to yet another possible connection between actin and microtubules at the cell periphery.

6 PROFILIN IN CENTROSOMAL MICROFILAMENT/MICROTUBULE CROSS-TALK

As reviewed above, an emerging body of data indicates that profilin on top of its established role for actin dynamics also plays a central function as a coordinating regulator of actin and microtubule (+)-end dynamics. This conjecture is now strongly emphasized by new data, demonstrating that profilin influences the nucleation of microtubules (Nejedlá et al., 2021). Therefore profilin emerges as a key component of the molecular interactome controlling the cytoarchitecture in mammalian cells. It was observed that profilin localizes to centrosomes and, following its depletion an increased nucleation of centrosomal microtubules was demonstrated. Profilin thus serves as a negative regulator of microtubule nucleation (Nejedlá et al., 2021). The γ-Tubulin ring complex (γ-TuRC) is the key component of centrosomal and non-centrosomal microtubule nucleation (Sulimenko et al., 2017). Therefore, it is interesting that profilin is observed to interact with γ-TuRC proteins, pointing to an intimate connection between profilin and this structure (Nejedlá et al., 2021).

Three laboratories recently have presented a high-resolution molecular structure of γ-TuRC (Consolati et al., 2020; Liu et al., 2020; Wieczorek, Huang, et al., 2020). Surprisingly these studies identified an actin-like molecule (Wieczorek, Huang, et al., 2020), subsequently identified as actin (Consolati et al., 2020; Liu et al., 2020) in the interior of the γ-TuRC. As revealed by cryoelectron microscopy (cryo-EM) reconstruction of native human γ-TuRC at 3.8 Å resolution, this actin molecule fitted into a connecting bridge spanning across the lumen of the cone-shaped structure (Wieczorek, Huang, et al., 2020; Wieczorek, Urnavicius, et al., 2020). In combination with crosslinking mass spectrometry analysis, the cryo-EM data further unveiled the molecular asymmetry of human γ-TuRC and detailed the actin presence in its internal core. It appears that actin and associated luminal factors, as well as mitotic-spindle organizing protein 2 (MTO2) at the outer perimeter of the assembly jointly are engaged in stabilizing the γTuRC spiral (Consolati et al., 2020). Additionally, cryo-EM analysis of γ-TuRC from Xenopus laevis at 4.8 Å resolution identified a 14-spoked arrangement of γ-Tubulin complex proteins (GCP) proteins and γ-tubulins in a partially flexible open left-handed spiral, and label-free mass spectrometry of purified γ-TuRCs identified actin as a bona fide structural component of the γ-TuRC in agreement with cryo-EM-data. Remarkably, treatment of purified γ-TuRCs with DNaseI, which binds the pointed (−)-end of the actin monomer with high affinity significantly inhibited microtubule nucleation activity, indicating that actin is of functional relevance for microtubule nucleation (Liu et al., 2020).

Based on the observations discussed above and since centrosomes have been proposed to nucleate actin polymerization (Farina et al., 2019; Inoue et al., 2019), it is possible that profilin loss results in less polymerization-ready actin (profilin-actin) available in the centrosomal region and, consequently, less of spatiotemporally controlled actin polymerization would occur similar to what was recently reported for the cell edge (Skruber et al., 2020). In this scenario, a reduced steric hindrance resulting from less of actin filaments in around centrosomes might open up for enhanced de novo microtubule nucleation from centrosomes due to less constrained space as has been proposed for mitotic centrosomes (Plessner et al., 2019). However, the recent observation of profilin-tuned microtubule nucleation at the centrosome (Nejedlá et al., 2021) was seen in interphase cells. Although it is possible that reduced actin polymerization in a constrained space still can account for the observation, an alternative reasoning where centrosomal profilin controls the availability of actin for γ-TuRCs is equally likely. Upon profilin deletion, more actin will become accessible for association with γ-TuRCs, which in turn would increase the formation of functional complexes and increase microtubule nucleation as documented by Nejedlá et al. (2021). It is noteworthy that the latter explanation also might apply for noncentrosomal microtubule nucleation, for example, from the Golgi (Cheng et al., 2019; Meiring et al., 2020) where profilin is present as well (Dong et al., 2000).

7 CONCLUSIONS AND FUTURE DIRECTIONS

As discussed above, recent observations points to the centrosome as combined actin- and microtubule organizing center with profilin taking a pivotal role as coordinator of the cellular distribution of the two force-generating fiber-systems. During directional migration, plasma membrane-associated actin turnover at the leading edge is strongly upregulated (Lai et al., 2008) and is dependent on recruitment of actin itself and actin regulatory proteins. Profilin-actin is recognized as a major source of polymerization-competent actin and is critical for actin-dependent protrusion activities (Faust et al., 2019; Funk et al., 2019; Grenklo et al., 2004; Lindberg et al., 2008; Skruber et al., 2020). Due to the rapid profilin and/or profilin-actin
FIGURE 2  Profilin regulates the organization of both actin and microtubules. The cartoon summarizes how profilin contributes to the arrangement of actin and microtubules in resting and moving cells as outlined in the text. In the stationary cell (left), profilin is balancing actin polymerization as well as microtubule nucleation and elongation along with other interacting components of the two cytoskeletal systems, actin (red) and tubulin (blue). Upon activation, as in the moving cell at right, profilin and profilin-actin become recruited to the advancing cell edge to support upregulation of actin turnover and formation of lamellipodia. Consequently, profilin concentration at the centrosome (yellow) and in other internal areas of the cell is lowered, which causes an increased nucleation of microtubules from the centrosome and possibly also from the Golgi-area (green). Moreover, the concomitant loss of profilin from microtubules results in an increased elongation rate with their (+)-ends tending to reach closer to the actin-rich arrangement underneath the plasma membrane (black).

recruitment to the plasma membrane, the profilin concentration is likely to be reduced in other parts of the cell. For the organization of microtubules this means that there will be both an increased nucleation of microtubules at the centrosome and a faster elongation of their (+)-ends towards the lamellipod at the periphery. Hence, centrosome profilin relocation dually affects microtubule organization by causing an increased number of microtubules to elongate with increased rate towards the cell edge as modeled in Figure 2. In other words, recruitment of profilin from central regions of the cell including the centrosome and Golgi area as well as from its location along microtubules not only augments actin turnover but simultaneously contributes to formation of more microtubules and their redirection towards the leading edge. We conclude that along with the cohort of other actin and microtubule interacting proteins that contribute to coordinate the two systems (Akhmanova & Steinmetz, 2010; Cheng et al., 2019; Juanes et al., 2020; Seetharaman & Etienne-Manneville, 2020) it appears that profilin with its dual control capacity with respect to both systems uniquely fits this process.

It will be exciting to follow the continued development of this cell biology area, with its many implications for cytoarchitecture, cell growth, and motility. Of particular interest is now to establish the molecular mechanisms by which profilin interferes with microtubule (+)-end dynamics and operates to control microtubule nucleation, and whether the interaction of profilin with γ-TuRC proteins depends on the γ-TuRC-associated actin or on other proteins, possibly with PLP-motifs that interact with γ-TuRC. Likewise, it will be important to establish if profilin affects microtubule nucleation from Golgi, and to what extent profilin 2 is involved during these microtubule-related processes. Clearly, the scene is now set for profilin studies to enter a new era.

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CONFLICT OF INTERESTS
The authors declare no conflict of interest, and apologize to those whose work was not cited despite relevance for the subject of the article.

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