Breast Cancer RESEARCH

VIEWPOINT

Profilin-1 versus profilin-2: two faces of the same coin?

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Abstract

Proteins belonging to the profilin family of actin-binding proteins are considered to be important control elements for actin polymerization and have been linked to a broad spectrum of cellular functions, including cell migration. An intriguing paper recently published in *Cancer Cell* unveils differential effects of profilin-1 and profilin-2, the two major isoforms of profilin, on actin cytoskeletal regulation, motility, and invasion of breast cancer cells, and further establishes a mechanism underlying profilin-2's suppressive effect on breast cancer cell migration. This viewpoint discusses the implications of these findings in the context of how profilins might regulate breast cancer cell motility.

Background

Membrane protrusion is the defining step of cell migration and requires dynamic regulation of actin polymerization at the leading edge involving orchestrated actions of different classes of actin-binding proteins. Actin assembly at the leading edge of migrating cells is thought to be facilitated by profilin's (Pfn's) interactions with G-actin and various promoters of actin nucleation and F-actin elongation [1,2]. The two major isoforms of Pfn, namely Pfn1 (the ubiquitously expressed form) and Pfn2 (a primarily neuronal-specific isoform that is also expressed at low levels in many other tissues) are structurally similar and can bind to similar sets of ligands (actin, phosphoinositides (PPIs), polyproline-domain containing proteins). However, isoform-specific differences exist in terms of binding affinity for various ligands [3]. This may explain why Pfn1 and Pfn2, despite having functional redundancy, can still serve distinct roles in actin-dependent processes, as shown in the context of regulation of neuronal architecture [4]. In their recent paper, Mouneimne and colleagues [5] investigated whether similar isoform-specific roles of Pfns exist in the context of cell migration.

Article

The authors reported that knockdown (KD) of Pfn2 in MCF10A (a normal mammary epithelial cell line) and SUM159 (an invasive but non-metastatic breast cancer cell (BCC) line with a Pfn1:Pfn2 ratio comparable to that of MCF10A cells) cells decreased F-actin bundling particularly at the regions near the leading edge, resulting in increased protrusive activities and faster migration/invasion *in vitro* and *in vivo*. Contrasting these phenotypic changes associated with Pfn2 KD, depletion of Pfn1 resulted in dramatically increased F-actin bundling, impaired membrane protrusion and defects in BCC migration/invasion *in vitro*. Even though Pfn1 KD did not suppress BCC invasion *in vivo*, the contrasting features of Pfn1 and Pfn2 KD cells *in vitro* led to the conclusion that these two Pfn isoforms can differentially regulate actin cytoskeletal reorganization and cell motility.

The anti-migratory effect of Pfn2 was further linked to increased actomyosin contractility requiring Pfn2:EVL (an Ena/VASP-like protein that has a much stronger affinity for Pfn2 than Pfn1) interaction. Finally, lower EVL expression and reduced F-actin density correlated with increased invasiveness and poor patient outcome in human breast cancer. As for Pfn2, only tumors that are low-invasive showed Pfn2 downregulation compared to non-invasive tumors but no significant difference in Pfn2 expression was noted between non-invasive and highly invasive tumors, further suggesting that the expression status of EVL but not Pfn2 could serve as an independent prognostic marker in breast cancer.

Viewpoint

A fundamental aspect of tumor cell invasion and metastasis is cell migration. Acquisition of a motile phenotype by tumor cells is typically associated with a disrupted actin cytoskeleton. Along this line, it was previously reported that Pfn1 expression is downregulated in a few

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different types of human cancer, including breast cancer [6,7]. We have found that lower Pfn1 expression correlates with increased metastatic propensity in human breast cancer, and furthermore, Pfn1 depletion in MDA-MB-231 cells (a metastatic BCC line) can actual enhance various dissemination-promoting activities (migration, extracellular matrix degradation and invasion, transendothelial migration) *in vitro* and vascular dissemination from tumor xenografts *in vivo* [8-10]. In light of this unconventional motility-suppressive function of Pfn1 in the pathological contexts, the study by Mouneimne and colleagues undoubtedly adds a new twist by bringing Pfn2 into the scenario and raises the following thought-provoking question in our mind: do Pfn isoforms have differential actions on actin polymerization and BCC motility in a strict sense or, alternatively, is the apparent isoform-specific differential phenotype a reflection of how other biological parameters ultimately influence the functional readouts of Pfn isoforms?

The major phenotypes associated with Pfn2 KD (loss of actin filaments, hypermotility) and Pfn2 overexpression (increased F-actin bundling, impaired motility) in SUM159 cells (Pfn1:Pfn2 molar ratio = 15:1) as found in this study essentially mirror those reported previously in response to Pfn1 KD and Pfn1 overexpression, respectively, in MDA-231 cells (this BCC line has almost negligible Pfn2 expression with a Pfn1:Pfn2 molar ratio >100:1 [5]). This suggests that there might not be a fundamental difference in how actin polymerization *per se* is regulated by the two Pfn isoforms. However, organization of those actin filaments into higher-ordered structures and its further impact on cell motility may be influenced by how actin is partitioned between different Pfn1 isoforms, the types of effectors utilized by Pfn isoforms in actin remodeling and the cellular abundance of those effectors, all of which can vary between cell types. Since Pfn-actin interaction is fine-tuned by phosphorylation [11], the post-translational modification status of Pfn isoforms may add an additional level of complexity. Finally, Pfn isoforms have markedly different binding affinities for PPI, an important negative regulator of Pfn-actin interaction [3]. Interestingly, at least, Pfn1 can influence cell motility through altering PPI signaling in an actin-independent fashion [12]. Therefore, the PPI signaling milieu in cells could also critically influence functional readouts of Pfn isoforms. Without having a comprehensive understanding of these additional biological influences, differential roles of Pfn isoforms in BCC motility in a true sense may be difficult to assess.

In summary, this is a highly interesting article that not only reveals a relatively less-studied member of the Ena/VASP protein family as a new prognostic marker for breast cancer, but also teaches an important lesson, that is, that Pfn2 function should no longer be ignored in non-neuronal cells even though it could be present at submicromolar concentrations.

Abbreviations
BCC, breast cancer cell; Ena, Enabled; EVL, Ena/VASP-like; KD, knockdown; Pfn, profilin; PPI, phosphoinositide; VASP, vasodilator stimulated phosphoprotein.

Competing interests
Dr Roy's laboratory works on profilin. The authors declare no other competing interests.

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