The filamins
Organizers of cell structure and function

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Abbreviations: FLNa, filamin A; IgFLN, immunoglobulin-like filamin repeat; ABP, actin-binding protein; ABD, actin-binding domain; GAP, GTPase-activating protein

Filamin A (FLNa), the first non-muscle actin filament cross-linking protein, was identified in 1975. Thirty-five years of FLNa research has revealed its structure in great detail, discovered its isoforms (FLNb and c), and identified over 90 binding partners including channels, receptors, intracellular signaling molecules, and even transcription factors. Due to this diversity, mutations in human FLN genes result in a wide range of anomalies with moderate to lethal consequences. This review focuses on the structure and functions of FLNa in cell migration and adhesion.

Introduction

Filamin A (FLNa) is the first actin filament cross-linking protein or gelation factor identified in non-muscle cells,1 and we now understand its structure in great detail. FLN is part of a family of three proteins (FLNb and c) that are products of distinct genes and are known to serve as scaffolds for over 90 binding partners including channels, receptors, intracellular signaling molecules, and even transcription factors (Table 1 summarizes the partners involved in cell adhesion and migration and Sup. Table 1 presents the other partners). Because of this extensive array of associated proteins, mutations in human FLN genes result in a wide range of cell and tissue anomalies.2-3 In this review, we focus on the structure and functions of FLNa in cell migration and adhesion. Other functions of FLNs are described in more detail in several recent review articles.4-6

Structure of FLNa

FLNa consists of two 280 kDa subunits that self-associate to form a 160 nm long semi-flexible strand (Fig. 1). Each FLN subunit has an N-terminal spectrin-related actin-binding domain (srABD) followed by 24 repeat β-pleated sheet units. Two intervening calpain-sensitive “hinges” separate the repeats into rod 1 (repeats 1–15), rod 2 (repeats 16–23) and the self-association domain (repeat 24).4-7 FLN repeats are Ig-like (IgFLN),8 each a β-barrel structure assembled from seven runs of (A-G) β-strands.9,10 The most C-terminal repeat, IgFLNa24, mediates dimerization and bestows a V-shape to the dimeric molecules11 that results in the perpendicular branching of F-actin12 (Fig. 1 and left part). A secondary F-actin-binding domain of lower affinity resides in the rod-1 segment of FLNa. Rod 2, on the other hand, does not interact with F-actin, leaving it free to associate with partner proteins, and most partner interactions occur within the rod 2 domain.12 Binding and positioning of multiple partners in close proximity on rod 2 facilitates signal transduction at FLNa-enriched sites in cells.

Detailed studies of purified FLNa and its subfragments in the electron microscope have shown rod 2 to have a folded structure (Fig. 1).12 Rod 1 is an extended chain. Its 58 nm contour length, encompassing Ig repeats 1–15, corresponds to the predicted end-to-end lengths of 15 IgFLNa repeats (3.5 nm each from the N-terminal to the C-terminal). However, the eight Ig repeats in the rod 2 domain (repeats 16–23) form a structure that is far more compact (19 nm) than those of rod 1 segments containing equivalent numbers of FLNa Ig repeats (Fig. 1). This compact structure is generated when the even-numbered repeats 16, 18 and 20 pair with neighboring repeats 17, 19 and 21, respectively (Fig. 2).12,13 For example, IgFLNa16 and 17 interact through their B-G and A-G faces, respectively, while strand A of IgFLNa16 protrudes from its normal position in the Ig domain and elongates hinge-1. Strands A of IgFLNa18 and 20 are also excluded from their normal positions and interact with the CD faces of neighboring IgFLNa19 and 21, respectively. As a result, the overall configuration of repeats in rod 2 is nonlinear providing rod 2 with a more globular structure. The exact configuration of paired repeats relative to each other in the rod 2 domain remains to be solved at the atomic level.

Structure of the FLNa-Partner Complex

The atomic structures of the binding interfaces between FLNa and GPIbα (a subunit of the GPIb complex or von Willebrand factor receptor), FLNa and the β integrin cytoplasmic tail or FilGAP and FLNa reveal that the C and D β-strands of the interacting IgFLNa repeats form a binding pocket for an opposing
Table 1. Filamin binding partners involved in cell adhesion, spreading and migration

| Partners          | Binding sites | Significance                                                                                                                                 |
|-------------------|---------------|--------------------------------------------------------------------------------------------------------------------------------------------|
| F-actin           | ABD, rod-1    | FLN induces orthogonal F-actin networks with unique mechanical and physiological properties[32]                                           |
| Calmodulin        | ABD           | Regulates F-actin binding in vitro[65]                                                                                                       |
| R-Ras             | 3             | Enhances integrin activation[94]                                                                                                             |
| Syk               | 5             | Flna is required for ITAM-mediated receptor signaling in platelet[29]                                                                       |
| Vimentin          | 1–8           | Expression of IgFLNa-1-8 restores spreading of filamin-deficient HEK-293 cells, vimentin phosphorylation, and the cell surface expression of β1 integrins[90] |
| Supervillin       | 8–10, 20–22   | Overexpression of IgFLNa8-10, but not 20–22 decreases spreading of Hela cells on fibronectin[200]                                              |
| Pro-Prion         | 10,16–18, 20, 21, 23 | FLNa interacts with the GPI anchor peptide signal sequence of pro-PrP that is expressed in some cancer cells  This interaction also promotes cell spreading and migration of melanoma cells[52,101] |
| FAP52(PASCIN2/Syndapin II) | 15–16 | Formation of focal adhesion[62]                                                                                                           |
| ECSM2             | 15–16, 19–21 | Endothelial chemotaxis and tube formation[103]                                                                                              |
| FILIP              | 15–18 | Downregulates FLNa and controls polarity and migration of neocortical cell[114]                                                            |
| GPIbα (CD42b)     | 17(A/B)       | Platelet adhesion and activation  Genomic instability[15,101,106]                                                                            |
| ICAM-1            | 19–24(A/B)    | Transendothelial migration  No binding to splice variant[1][107]                                                                             |
| Integrin β        | 21 (A/B/C) | Adhesion  Mechanoprotection  Negative regulation of integrin activation[15,107]                                                              |
| Migfilin (FBLP-1) | 21 (A/B/C), 10–13 (B) | Disconnects FLNa from integrin and promotes talin-integrin binding[15,18,108,109]                                                             |
| Sphingosine kinase 1 | 22–24 | FLNa-dependent kinase activity[110]                                                                                                           |
| Tissue Factor     | 22–24         | Phosphorylation of TF enhances the interaction[111]                                                                                        |
| CEACAM1 (CD66a)   | 23–24         | Reduces cell migration[112]                                                                                                                  |
| Trio              | 23–24         | GEF for RhoG/Rac1 and RhoA  Required for ruffling[62]                                                                                       |
| FilGAP            | 23 (A specific) | Rho- and ROCK-regulated GAP for Rac. FLNa-binding is required for cell spreading and stimulates GAP activity[19,96]                      |
| Rho               | 24            | Remodeling of cytoskeleton[113]                                                                                                              |
| Rac               | 24 (B: 20–21) | Remodeling of cytoskeleton[113–115]                                                                                                        |
| Cdc42             | 24            | Filopodia formation[113]                                                                                                                    |
| RalA              | 24            | Remodeling of cytoskeleton[116]                                                                                                              |
| ROCK              | 24            | Remodeling of cytoskeleton[116]                                                                                                              |
| FILIP-1L (downregulated in ovarian cancer 1)** | ? | Overexpression of FILIP1L inhibits cell proliferation and migration and increased apoptosis[117]                                           |
| IKAP (ELP1)       | ?             | Loss-of-function mutations in the IKBKAP gene, which encodes IKAP, cause familial dysautonomia[118]                                          |
| Lbc**             | ?             | RhoGEF                                                                                                                                    |
| P190RhoGAP**      | ?             | Expression of calpain-insensitive FLNa excludes p190RhoGAP from the lipid raft, thereby increase Rho activity[46]                        |
| Vav-2**           | ?(B)          | Guanine nucleotide exchange factor for the Rho family Complexes with Rac[111,114]                                                           |
| p311**            | ?             | Highly expressed in invasive glioma cells and enhances glioma cell migration[200]                                                            |

*Binding site on FLNa from N-terminal (top) to C-terminal (bottom) unless otherwise noted, ” direct interaction has not been confirmed, cytoskeleton (red), small GTP-binding proteins and their regulators (yellow), kinases (green), transmembrane proteins (cyan), others (white).
β-strand, donated by the binding partner (Fig. 2). In similar fashion, the FLaNA binding sites in migfilin, CFTR (cystic fibrosis transmembrane conductance regulator), and pro-prion protein are related to those of GPIbα, β integrins and FilGAP. Each binding interface is a β-strand run of nine residues that can correctively position itself in the CD repeat groove of a FLaNA repeat (Fig. 2). Alternating residues of these β-strands, thus, either face or look away from the groove. Those facing the groove are restricted to hydrophobic amino acids, which suggests primarily a hydrophobic interaction.

A single binding event between FLaNA and a given binding partner, however, fails to account for the measured binding specificity or strength of the native proteins’ interaction. For example, a GPIbα peptide containing all the FLaNA binding sequence binds to not one but seven FLaNA repeats (IgFLNa 4, 9, 12, 17, 19, 21 and 23) that are structurally similar, although point mutations in IgFLNa17 in full-length FLaNA are sufficient to disrupt all binding to the GPIb complex when it is expressed in CHO cells. The same holds true for the FLaNA-binding site of FilGAP which is similar to that of other binding partners, and potentially interacts with other repeats, although FilGAP binds only to IgFLNa23 in cells. Thus, there are structural features in the intact FLaNA molecule or in the partner molecule that limit this promiscuous binding. Establishment of high affinity interactions between FLaNA and partners requires binding between two or more binding sites, i.e., one on each FLaNA subunit and two on the partner protein, as the binding affinities, determined with peptides encompassing the binding strands of GPIbα, β integrins or FilGAP, for an individual FLaNA Ig repeat are weak. Taken together, the quaternary structure made by FLaNA bound to its partner protein, therefore, defines the overall binding specificity and strength. Thus, bivalent reagents should be considered when designing inhibitors for partner binding sites.

Since the CD faces of repeats 19 and 21 that are used to bind the integrin cytoplasmic tail or other partner proteins are occupied with strands A of their precedent repeats (Fig. 2), binding of partners within these cryptic sites may require conformational changes in the rod 2 domain. The CD faces of repeats 17 and 23, on the other hand, which interact with the GPIb complex and FilGAP, respectively, are not masked. Partner binding to and between the two FLaNA subunits may also crosslink the FLaNA molecule and stabilize its structure.

**Regulation of FLaNA-Partner Interactions**

FLA-na-partner interactions are regulated by: (1) mechanical forces, (2) phosphorylation, (3) proteolysis, (4) competition between binding partners and/or (5) multimerization of partners.

**Mechanical force-induced conformational changes.** Insight into the molecular structure of FLaNA, its abundant C-terminal binding and interacting partners, and its mode of binding F-actin...
Consistent with these negative results, a molecular dynamics simulation suggested that phosphorylation at Ser2152 does not impact the "opening" of the cryptic integrin binding site of repeat 21 by mechanical force. In contrast, a recent computer simulation concluded that this phosphorylation event might facilitate force-induced dissociation of auto inhibition by decreasing the force requirement.

Phosphorylation of partners’ binding sites can also regulate their interaction with FLNa. Phosphorylation of the integrin β2 tail on Thr758 dissociates it from FLNa and promotes binding of 14-3-3 and talin to the integrin, thereby maintaining it in an active state. Proteolysis. Cleavage within the two hinges of FLNa by calpain generates rod1, rod2 and self-association domain (repeat 24) subfragments. Following proteolysis, C-terminal-derived FLNa fragments (IgFLNa16–23 or 16–24) translocate to the nucleus together with FLNa-binding transcription factors such as androgen receptor and FOXC1. Catastrophic proteolysis of FLN is mediated by an ankyrin repeat-containing protein with a suppressor of cytokine signaling box 2 (ASB2), which targets FLNs for proteosomal degradation at discrete stages of development and differentiation in cells. Proteolysis of FLN by calpain or ASB2 inhibits cell spreading, but not migration, presumably by altering the dynamics of focal adhesions.

Competition with other molecules. All FLN isotypes interact with β integrin cytoplasmic tails albeit with different affinities, which can be predicted by their atomic structures. The FLN-binding site on integrin overlaps the site used by other integrin-binding proteins such as talin, kindlins, β3 endonexin, ICAP1.
14-3-3, CD98 and Shc. Conversely, certain FLN-binding partners such as migfilin compete with the integrin for repeat 21 binding (Table 1 and Sup. Table S1). Therefore, partner competition for FLN or for the integrin tail regulate focal adhesion complexes making the expression profile and concentration of each reactant critical in understanding focal adhesion turnover.

Oligomerization and/or clustering of partners. While the topology of the binding groove in the FLNa repeat and that on opposing partner β-strand site determines the binding kinetics for a given site, high avidity binding requires engagement of two or more sites as discussed above: binding interactions with both FLNa subunits greatly increase binding avidities by ~100 fold. For example, the k on for the binding of polypeptide mimics of the GPIbα and FilGAP binding to IgFLNa17 and IgFLN23, respectively, are over 10 μM. However, the binding affinity of the von Willebrand receptor complex for FLNa or FilGAP to FLNa are estimated for other experiments to be at 100 nM and ~200 nM. In similar fashion, integrins clustered at focal adhesion sites may generate much higher avidities for FLNa. Partner oligomerization through clustering, therefore, can potentially regulate the interaction with FLNa.

**Filamin Mutations and Diseases**

FLNa, encoded on the X chromosome, is the most abundant and widely distributed member of the filamin family proteins. FLNb, a nonmuscle filamin, is encoded on human chromosome 3. The FLNc gene resides on chromosome 7, and is expressed primarily in adult cardiac, smooth and striated muscle tissues. FLN isoforms have both common and distinctive binding partners and features in their structures, expression level and localization. Mutations and deletions in the FLN genes that prevent normal FLN protein expression result in wide range of congenital anomalies. FLN mutations are also common in human breast and colon cancers. Nuclear FLNa fragments produced by proteolysis are significantly more abundant in benign prostate than metastatic prostate cancers. Additionally, FLNa mutations have been identified as the cause of the most common genetic heart valve disorder, familial cardiac valvular dystrophy. In mice, complete loss of Flna expression causes embryonic lethality with severe defects in cardiovascular formation and bone development. Mutations or deletions of FLN orthologs in other organisms, such as Dicyostelium, Drosophila and C. elegans, also result in developmental defects. Since numerous binding partners interact with FLNs (Table 1 and Sup. Table S1), the pathological mechanisms of the diseases are most likely attributed to loss of partner binding or aberrant interactions caused by mutations. However, the effect of most of these mutations on partner interactions remains to be elucidated at the molecular level.

**Role of FLNa in Cell Mechanics**

Cell adhesion and migration inevitably rely on active and reversible changes in the mechanical properties of cells. Leukocytes, for example, need to generate internal force to crawl through connective tissues to hunt and ingest pathogens. Cells also respond to external mechanical forces imposed by their environment. Vascular cells undergo morphological changes in response to alterations in the fluid and mechanical shear stresses that are imparted on their apical surface by blood flow and their basolateral surfaces by pulsatile vascular stretch and retraction, and these responses have profound implications in the physiological function of blood vessels, and can lead to disorders such as atherosclerosis and thrombosis. In addition, depending on the stiffness of substrates, stem cells differentiate into distinct cells. Therefore, understanding of cell mechanics is essential for elucidating many of the fundamental aspects of cell behavior from motility to differentiation and development.

Unlike most conventional materials, cells behave in a highly nonlinear fashion (strain vs. stress) as strain increases. When a small force is applied on a short time scale, cells deform linearly and reversibly in proportion to the applied force. However, as the strain increases, cells deform less, a process called “strain-stiffening,” which extends the range of forces a cell can endure before undergoing mechanical collapse. When a relatively small continuous stress is applied on longer time scale, cells respond by deforming slowly and irreversibly. These behaviors demonstrate that cells have both elastic and viscous characteristics, and behaves as nonlinear viscoelastic materials.

The mechanical properties of cells are generated by the combined interactions of the cytoskeletal elements. One of the
polymer systems, filamentous actin, concentrates underneath the plasma membrane and is necessary for both cell motility and the maintenance of cell shape. Purified F-actin forms entangled networks in solution that deform linearly. Hence, additional cohesive proteins are required to stiffen the networks to reconstitute cell like properties. ABPs that can cross-link actin filaments account for this discrepancy. FLNa-actin networks reconstitute many aspects of cell mechanics. They behave as weak elastic solids under low shear stress due to the flexible nature of actin-FLNa crosslinks, yet can support large shear stresses and have pronounced nonlinear strain-stiffening behaviors. These mechanical properties are attributed to FLNa's unique structure and how it interacts with F-actin to form orthogonal branches. High avidity binding to F-actin due to dimerization and multiple binding to F-actin through FLNa ABD and rod 1 confers strain-stiffening on actin networks. The hinges account for the flexibility of FLNa molecule. Orthogonal branching is the most efficient way to form the largest volume of actin gel with a minimal of material to support cellular integrity.

### Effect of Genetic Loss of Filamin on Cell Migration and Development

Cultured FLNa-deficient melanoma cells fail to polarize and move because they have highly unstable surfaces that continuously expand and contract circumferential blebs. Restoring normal levels of FLNa in these deficient cells rescues motility. In humans, null mutations in the FLNa gene disrupt long-range directed neuronal migration within the cerebral cortex in X-linked periventricular heterotopia. Overexpression of Flna can also prevent migration, presumably by sequestering signaling molecules from their normal position and by altering F-actin and focal adhesion turnover to enhance adhesion. Flna knock-out mice, however, do not develop periventricular heterotopia, and embryonic fibroblasts isolated from these animals do not bleb or have defects in migration and growth. Since FLNb is also ubiquitously expressed in these cells, FLNc is expressed in some nonmuscle cells during development and many FLNa-binding partners also interact with these isoforms (Table 1 and Sup. Table 1), they could compensate for FLNa deficiency. In fact, expression of an shRNA-resistant FLNa in FLNab double knockdown cells completely rescues their spreading defect. However, even some FLNa knockdown cells migrate at speeds comparable to wild-type cells once they overcome their diminished ability to spread on substrates and become attached. Whether this is due to the residual expression of other FLN isotypes, or if there is a FLN-independent migration mode, remains to be elucidated. Additionally, developmental differences between humans and mice should also be considered. The mouse brain is small and less complex than its human counterpart. Neuronal migration in humans may also require different cues. However, Flna-null mice do exhibit a thinning of the cerebral cortex that may indicate a migration defect.

### Cooperation of Filamin with its Partners in Cell Adhesion and Migration

FLN-binding partners interactions regulate cell adhesion, spreading and migration (Table 1 and Fig. 4). The molecular mechanism by which FLN coordinates these partners is complex. Directed migration requires temporal polarization and spatial enrichment of molecules at specific sites. How does FLN, particularly when bound to actin that is dispersed through cells, perform this task? Immunofluorescent microscopy reveals FLNa and b to be enriched at the cell periphery and in the focal adhesions of cultured cells, while FLNc localizes in the muscle Z-disc. One mechanism for the enrichment of FLNs at these sites is their recruitment by binding partners, such as receptors and adhesion molecules that preferentially reside at these sites (Fig. 4). A second mechanism concentrating FLNa in newly assembled actin networks in lamellipodia occurs because of higher avidity for the branched F-actin junctions in these regions (Fig. 4). FLNa recruitment by one partner could allow it to scaffold additional signaling molecules and enhance the efficiency of signal transduction. In addition, while FLN-binding partners may potentially collect FLN molecules to specific locations within the cell, their function may require the recruitment of additional partners by FLNa. It is unlikely that all FLN-binding partners are expressed by a given cell, as partner expression levels are tightly regulated in different cells and/or different developmental stages (Table 1 and Sup. Table 1). Therefore, the phenotype of FLN mutations must be studied within different cell types and/or developmental stages.

### Role of Filamin in Integrin-Dependent Cell Adhesion and Migration

Although certain cells can migrate without integrins or swim without attaching to a substrate, most cells migrate in an integrin-dependent manner. Our current understanding of integrin function at focal adhesions in moving cells is summarized in Figure 4. Since depletion of FLN results in integrin activation, FLN appears to act primarily as a negative regulator of integrin activation. Therefore, any event that alters the FLN-integrin binding affects integrin activation status. Consistent with this notion, diminished expression of FLNa increases the invasiveness of human breast cancer cells. Since FLNa silencing also induces activation of calpain, which leads to degradation of focal adhesion proteins, suppression of FLNa expression may facilitate focal adhesion turnover, thereby promoting the invasion. Recycling of integrin is also essential for sustained cell migration. The trafficking of β1 integrins to the cell membrane is regulated by PKCε-mediated phosphorylation of vimentin bound on the N-terminal of FLNa, as vimentin phosphorylation is impaired in FLNa knockdown cells. Taken together, FLN regulates not only integrin activation, but also its recycling to coordinate integrin-dependent migration.

Despite increasing evidence supporting a FLN's suppressor function for integrin activation, degradation of FLN is not
likely to be the only mechanism to affect cell migration, and it is not surprising that an opposite effect of FLNa expression on cell migration has been reported. This result indicates that the role of FLN in cell migration is cell type-dependent and that balanced FLNa/integrin interactions generate normal cell adhesion and migration.

**Does FLNa Regulate Blebbing Migration?**

Blebbing has recently received renewed attention in motility, as cancer cells can switch between mesenchymal (elongated) and amoeboid (blebbing or rounded) migration modes in three-dimensional environments. Since amoeboid cells can squeeze into the extracellular matrix, these cells escape and metastasize. Elucidating blebbing mechanisms and the conversion between migration modes is therefore of great importance.

Blebbing is believed to initiate following local disruption of plasma membrane-F-actin interactions and occurs because cells are under internal hydrostatic pressure powered by myosin contraction, as blebbistatin, a myosin II inhibitor, quenches most cellular blebbing. Blebbing is a prominent feature of FLNa-deficient melanoma cells that have weak cortical actin networks. In normal cells, both Ca activation-gelsolin and Ca-calmodulin signaling can reduce stiffness of an FLNa-actin gel. The blebbing mode is also regulated by the RhoA-ROCK pathway that induces myosin contraction and antagonizes the Rac1-WAVE pathway, which induces actin polymerization-dependent protrusions (mesenchymal migration mode). Suppression of Rac1 activity is catalyzed by ARHGAP22 whose activity is regulated by actinomyosin contractility through an unknown mechanism, rather than by direct phosphorylation by ROCK. Given that overexpression of FilGAP (ARHGAP24), a Rac-specific GAP that interacts with FLNa, induces blebbing, and that the FLNa-FilGAP interaction is potentially regulated by mechanical force, force-induced regulation of the FLNa-FilGAP interaction could provide a simple mechanism for the conversion between mesenchymal and amoeboid migration modes.

**Conclusion and Outlook**

Since its discovery in 1975, studies on FLN have substantially advanced an understanding of its structure and functions.
Nevertheless, important questions still remain: (1) How many of the FLN-partner interactions are regulated? (2) What is the quaternary structure formed between FLN and partners? and (3) What are the biochemical mechanisms of disease caused by FLN mutations? Disease-causing mutations distribute throughout the FLN molecule, but why do only a small number of binding partners interact in FLN’s N-terminal rod 1 domain, although repeat 10 is a mutational hot spot?3

The schematic FLNa model depicted in Figure 1 is consistent with all currently reported data. However, a more detailed structural analysis of FLNs, particularly complexed with partners, is required to understand how FLN mutations cause disease. Structural information will enable investigators to generate point mutations in FLNs or their partner proteins that lack only partner-specific related activity. Probing cell function with these molecules in vivo will provide deeper understanding of the dynamics of FLN-partner interaction during migration.

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Note

Supplemental materials can be found at: www.landesbioscience.com/journals/celladhesion/article/14401

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