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FH proteins as cytoskeletal organizers

Steven Wasserman

Regulation of cell shape is a poorly understood yet central issue in cell biology. Recent experiments indicate that FH proteins link cellular signalling pathways to changes in cell shape. Members of the FH protein family play essential roles in cytokinesis and in driving alterations in cell polarity. This review discusses the structure and function of these proteins and examines the evidence that they interact specifically with Rho GTPases and profilin to organize the actin-based cytoskeleton.

Both mitosis and meiosis require the spatial and temporal coordination of cytokinesis with nuclear division. The recently discovered FH (formin homology) protein family appears to play a crucial role in this coordination, mediating formation or stabilization of the contractile ring. More generally, FH proteins participate in a range of actin-mediated processes affecting cell polarity and shape. There is now a substantial body of evidence indicating that FH proteins fulfil these functions by interacting, through distinct domains, with the actin-binding protein profilin and GTP-binding proteins of the Rho family.

FH protein structure

The FH proteins were defined[1,2] on the basis of conservation in sequence and protein organization among two *Drosophila melanogaster* proteins, DIAPHANOUS (DIA) and CAPPUCCINO (CAPU), a yeast protein, Bni1p, and a mouse protein, formin. Subsequently, additional genes encoding FH proteins have been found in fungi, plants, worms and mammals; there are now nearly a dozen characterized family members (Table 1). FH proteins are 1000 to 2000 amino acids (aa) in size and contain two conserved sequence domains, termed FH1 and FH2 (Fig. 1)[1]. FH1 domains average ~100 aa in length, and most are extremely proline rich, with multiple stretches of consecutive proline residues. FH2 domains are conserved regions of ~130 residues found only among members of the FH protein family.

The FH1 and FH2 domains in all family members are separated by ~160 aa, whereas the lengths of the flanking regions vary considerably. Blocks of sequence similarity within these variably sized regions have become recognizable as the number of known family members has increased. For example, searches with the PIMA algorithm[3] reveal two blocks of conserved sequence within the N-termini of many FH proteins (Fig. 2). Sequence conservation has also been detected in regions surrounding the FH2 domain[4,5].

All of the FH proteins other than CAPU contain one or more coiled-coil regions, as predicted by the NEWCOILS and PAIRCOILS algorithms[6]. Typically, one coiled-coil region lies N-terminal to the FH1 domain, and one or two lie within or C-terminal to the FH2 region (Fig. 1). Coiled-coil domains are common among cytoskeletal proteins and provide the potential for homotypic and heterotypic interactions.

Database searches with a consensus FH2 domain indicate that eukaryotes contain multiple FH genes

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TABLE 1 – FH PROTEIN FAMILY MEMBERS

Protein	Species	Cellular functions	Pairing partners[a]	Accession no.	Refs
Bni1p	*S. cerevisiae*	Cytokinesis; cell polarity	Profilin, Rho1p, Cdc42p, Bud6p/Aip3p	Z71547	10,11,13,37
Bnr1p	*S. cerevisiae*	Cytokinesis; cell polarity	Profilin, Rho4p	Z47047	14
cdc12	*S. pombe*	Cytokinesis	Profilin	Z68136	5
fus1	*S. pombe*	Cell polarity		L37838	7
SepA	*A. nidulans*	Cytokinesis; cell polarity		U83658	4
	A. thaliana			Z97338	
CYK-1	*C. elegans*	Cytokinesis		U40187	–[b]
CAPU	*D. melanogaster*	Cell polarity	Profilin	U34258	2,9
DIA	*D. melanogaster*	Cytokinesis	Profilin	U11288	1,18,–[c]
mDia	*M. musculus*		Profilin, Rho	U96963	19
hDIA	*H. sapiens*				15
Formin	*M. musculus*		WW motifs, SH3 domains	X62379	24,32

[a]Endogenous interactions with the pairing partners listed have been confirmed only for the yeast FH proteins.
[b]B. Bowerman, pers. commun.
[c]B. Gish, pers. commun.
Abbreviations: *A. nidulans, Aspergillus nidulans*; *A. thaliana, Arabidopsis thaliana*; CAPU, CAPPUCCINO; *C. elegans, Caenorhabditis elegans*; DIA, DIAPHANOUS; *D. melanogaster, Drosophila melanogaster*; FH, formin homology; *H. sapiens, Homo sapiens*; *M. musculus, Mus musculus*; *S. cerevisiae, Saccharomyces cerevisiae*; *S. pombe, Schizosaccharomyces pombe*; SH3, Src-homology 3.

(Table 1; S. Wasserman, unpublished). In *Saccharomyces cerevisiae*, the only eukaryote for which a complete genome sequence is available, there are two recognizable FH genes (*BNI1* and *BNR1*), whereas there are at least three in some other species (e.g. sequences U40187, U88314 and Z78013 in *Caenorhabditis elegans*). Although the two FH genes in *S. cerevisiae* overlap in function, the same does not appear to be true for the pairs of genetically identified FH genes in flies and fission yeast (Table 1).

FH proteins play multiple roles in organizing the actin cytoskeleton

Phenotypic analyses of recessive mutations have demonstrated an essential role for FH genes in cytokinesis in flies[1], worms (B. Bowerman, pers. commun.) and fungi[4,5]. *Drosophila dia* alleles conferring a partial loss of gene function cause a failure in cytokinesis during germ cell proliferation in adult males; null mutations are lethal during development and result in the production of highly polyploid cells. Characterization of the maternal-effect-lethal *cyk-1* mutation in nematodes has revealed that cleavage furrows are properly situated but regress soon after each nuclear division, generating a multinucleate unicellular embryo. *Schizosaccharomyces pombe* cells mutant for *cdc12* have a wild-type actin cytoskeleton during interphase but display delocalized actin patches in place of an actin ring during mitosis. FH proteins thus appear to have an evolutionarily conserved role in cytoskeletal organization during cytokinesis.

FH proteins function not only in cytokinesis but also in redefining cell polarity through alterations in the actin-based cytoskeleton. The *fus1* gene of *S. pombe* is required for fusion of the mating projections of conjugating cells[7], a process that is, in principle, the reverse of cytokinesis. Mutations in the *capu* locus of *Drosophila* alter vectorial, microtubule-based cytoplasmic streaming[8] but appear to do this indirectly, through a disruption of the actin cytoskeleton[9]. The budding yeast gene *BNI1* participates in the polarity-dependent processes of bud-site selection and cytoskeleton-mediated RNA localization, as well as cytokinesis[10–14].

The recent finding that a defect in a human homologue of *diaphanous* is the cause of an autosomal dominant hearing disorder suggests that the repertoire of cytoskeletal processes mediated by FH proteins is not yet fully known. A splice-site mutation altering the C-terminal 52 amino acids of hDIA1 is responsible for the bilateral deafness affecting 78 of 147 adult members of an extended Costa Rican family[15]. Likely targets for hDIA1 action are the hair cells of the cochlea, which rely on actin filament arrays to detect and amplify acoustic stimulation[16]. Consistent with the hypothesis that a disruption of the hair cell cytoskeleton is responsible for the hearing loss caused by an hDIA1 defect, two other deafness loci have been found to encode unconventional myosin molecules (reviewed in Ref. 17).

FH proteins localize to specific cytoskeletal structures

In all species examined, the localization of FH proteins correlates with gene function and is a distinct subset of the pattern of localization observed for actin. For example, in *S. pombe* cells entering mitosis, cdc12 appears as a circle coincident with the cell division ring (Fig. 3a)[5]. The cdc12 ring increases in intensity during anaphase, then contracts (Fig. 3b–d). Fly and mouse Dia concentrate in the cleavage furrows of dividing cells (Refs 18 and 19; B. Gish and S. A. Wasserman, unpublished). Other structures to which FH proteins specifically localize include the membrane ruffles of motile cells (mDia) and the mating projections of yeast (fus1 and Bni1p)[7,13,19].

There is evidence that FH proteins that participate in cytokinesis are recruited to the division site early in the process of ring assembly. In interphase *S. pombe* cells expressing high levels of cdc12, immunolocalization studies reveal a discrete spot of cdc12 at a medial position corresponding to the site of actin ring formation[5]. A spot of similar size and location results from overexpression of another component of the *S. pombe* actin ring, the Myo2 type II myosin heavy chain[20]. Thus, a complex containing cdc12 and Myo2p appears to mark the cleavage plane prior to the assembly of an actin ring.

There is some evidence that the vertebrate formins, unlike other FH proteins, localize to and function in the nucleus[21–23]. That mutations in the murine *formin* locus cause kidney aplasia and oligodactyly has been interpreted in terms of a determinative role in developmental patterning, consistent with a nuclear site of action[24,25]. However, kidney aplasia and oligodactyly also result from mutations in the *Os* gene, a mouse locus with an essential role in cell division[26]. Furthermore, experiments with embryonic fibroblasts indicate that chick formin is not associated with chromatin during mitosis[21]. It is conceivable, therefore, that the vertebrate formins are required for a cytoskeleton-mediated step in cell division and that the apparent functional disparity between the formins and other FH proteins is illusory.

FH proteins interact directly with profilin

Based on a genetic and molecular characterization of *diaphanous* from *Drosophila*, it was proposed that FH1 domains might bind *in vivo* to profilin, a known regulator of actin polymerization[1]. Loss-of-function mutations in genes encoding profilin disrupt cytokinesis in *S. cerevisiae*, *S. pombe* and *D. melanogaster*[27–29]. Indeed, mutations in *chickadee*, the *Drosophila* profilin locus, resemble *dia* mutations in their male germline phenotype[30]. Furthermore, profilin binds to homopolymeric proline sequences[31], such as those in FH1 domains (see Fig. 1).

The ability of profilin to bind to FH proteins has been confirmed by both two-hybrid experiments and *in vitro* binding studies carried out with fly, yeast and human proteins (see Table 1). In the case of both Bni1p and Bnr1p, structure–function deletion analysis mapped the profilin-interacting region to the FH1 domain, and, more specifically, to a 50-aa region that begins and ends with a homopolymeric proline sequence[13,14]. Consistent with these findings, a mutant form of profilin that binds to actin but not poly-L-proline fails to interact with Bni1p in a two-hybrid assay[13]. Moreover, poly-L-proline competes with cdc12 for binding to *S. pombe* profilin[5].

Genetic-interaction studies in yeast have explored the *in vivo* significance of the *in vitro* interaction between profilin and FH proteins. In *S. pombe*, cells mutant at both the profilin (*cdc3*) and FH protein (*cdc12*) loci have a phenotype much more severe than that of either single mutant[5]. In *S. cerevisiae*, increased expression of the wild-type *PFY1* profilin gene suppresses the growth defects caused by a dominant-negative *bni1* construct[13]. Together with the molecular and biochemical data discussed above, these results provide strong evidence for an interaction between wild-type FH proteins and profilin in both fission and budding yeast.

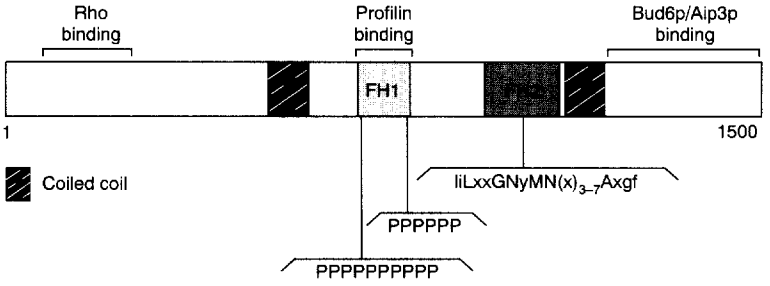

FIGURE 1

FH protein structure. Scale drawing of a generic FH protein, 1500 amino acids in length, indicating the position of the FH1 and FH2 domains, two coiled-coil domains and the binding sites for proteins of the Rho, profilin and Bud6p families. The two homopolymeric proline sequences are characteristic of the FH1 domain. The sequence listed below the FH2 domain represents the most highly conserved portion of this domain. Upper-case letters indicate residues with little or no sequence variation, with the indicated residue being common to at least 90% of the FH proteins. Lower-case letters indicate limited sequence variation, with the residue indicated being present at a frequency of at least 50%. Positions marked with an 'x' have substantial sequence variation.

The FH1 domains of formins have been shown to interact *in vitro* with both Src-homology 3 (SH3) and WW domains, two motifs that interact with proline-rich target sequences[32]. Interaction with proteins containing SH3 or WW motifs might link vertebrate formins and perhaps other FH family members to the cytoskeleton or might regulate the interaction of FH1 domains with profilin[14]. However, FH proteins have not been shown to bind to SH3 or WW domains *in vivo*.

FH proteins interact with additional actin-binding proteins

Bni1p can bind to at least one cytoskeletal component, the Bud6 or Aip3 protein, in addition to profilin[13]. Bud6p, an actin-binding protein required

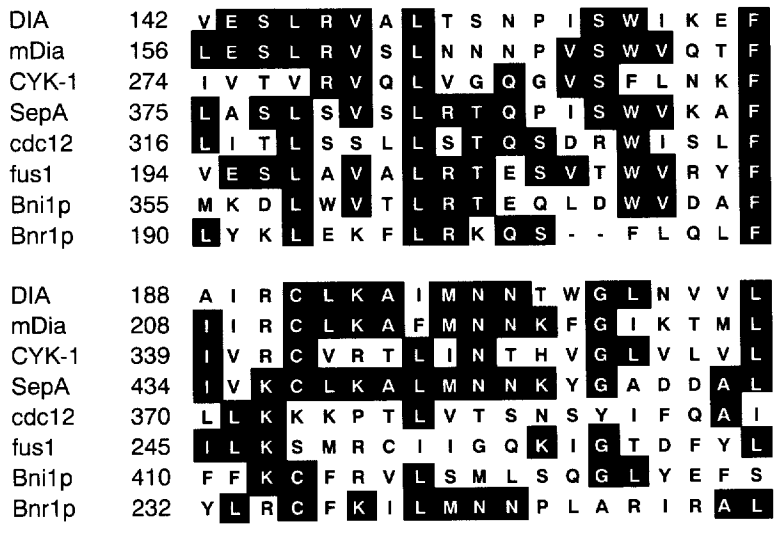

FIGURE 2

Sequence conservation in N-terminal regions of FH proteins. Sequences were aligned using the PIMA algorithm[3]. Boxed amino acids are identical among at least three of the FH proteins shown. Numbers indicate the position of the first residue in each row relative to the amino acid sequence of the indicated protein.

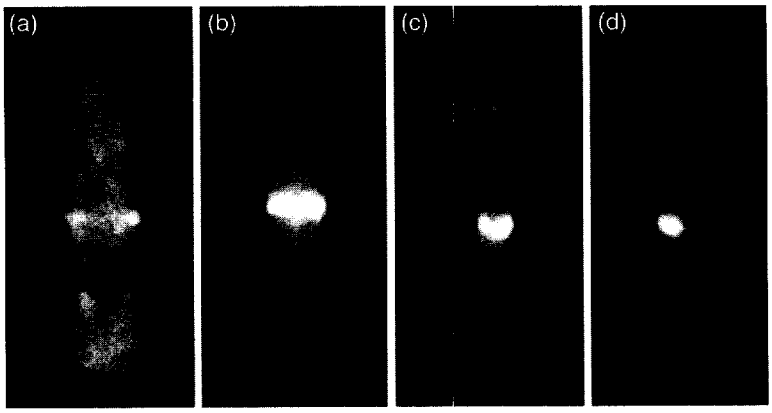

FIGURE 3

cdc12 localizes to the cell-division ring in wild-type cells. *Schizosaccharomyces pombe* cells were fixed and processed for immunofluorescence using an antibody against cdc12 as described in Ref. 5. (a) early mitosis, (b) early anaphase, (c) midanaphase and (d) postanaphase. Photomicrographs courtesy of F. Chang, Columbia University, USA.

for wild-type cytoskeletal polarity in *S. cerevisiae*[33], binds to the C-terminal portion of Bni1p, outside of the FH2 domain (see Fig. 1). The similarity in loss-of-function phenotypes between *bud6* and *bni1* mutants, the colocalization of the wild-type gene products and the binding data all support the hypothesis that these proteins act together *in vivo* in reorganization of the actin cytoskeleton[13].

FH proteins contain a novel Rho-binding domain

Just as profilin functionally connects FH proteins and the actin cytoskeleton, there is good evidence that members of the Rho subfamily of GTP-binding proteins link FH proteins to cellular signalling pathways. Rho proteins, Ras-related GTPases, regulate cell adhesion, motility, bud-site selection and contractile processes[34,35]. The Rho subfamily includes the Rho, Rac and Cdc42 proteins, of which both Rho and Cdc42 are required for cytokinesis[36]. It is these two proteins that interact with members of the FH family.

Two-hybrid screens with constitutively active forms of yeast Rho1p and mouse RhoA identified the FH proteins Bni1p and mDia, respectively, as Rho interaction partners[19,37]; a pairwise interaction assay demonstrated that Bni1p also binds to Cdc42p[13]. Studies with wild-type and mutant forms of RhoA, Rho1p and Cdc42p indicate that the mouse and yeast FH proteins interact preferentially with the activated, or GTP-bound form, of these Rho subfamily members. Furthermore, *rho* mutations display a strong genetic interaction (synthetic lethality) with *bni1* mutations[19,37], supporting the hypothesis that the gene products associate functionally *in vivo*.

In general, Rho proteins are capable of organizing the actin cytoskeleton through multiprotein complexes at specific sites within the cell. They differ from one another in which proteins they recruit, at which particular sites they function and in which stage of the cell cycle they are active[35]. Some of this specificity could derive from interactions with FH proteins. For example, in *S. cerevisiae*, the two FH proteins have distinct and specific pairing partners. Bnr1p binds to Rho4p but not three other Rho proteins[14], whereas Bni1p interacts with Rho1p and Cdc42p[13,37].

A Rho-binding site has been mapped to the N-terminal portion of three FH proteins[14,19,37], although no consensus Rho-binding site has been identified among these family members. The N-terminal motifs illustrated in Figure 2 fall within the interaction domains defined for Bnr1p (63–421) and mDia (aa 63–260) but not for Bni1p (aa 90–343).

FH protein function in cytokinesis

In modelling cytokinesis, it is tempting to speculate that FH proteins are recruited to specific sites by activated Rho and in turn recruit profilin to these sites. Profilin could then regulate the formation, stabilization or function of the contractile ring through its effect on actin polymerization[38]. The interactions among Rho, FH proteins and profilin might therefore be required for assembly or contraction of the actin-based cleavage ring during cytokinesis as well as for maintaining ring integrity during contraction. For Rho, it is known that gene function is required throughout cell division; inhibition of Rho activity both blocks and aborts cytokinesis; pre-existing contractile rings disappear, whereas cortical actin organization is undisturbed (reviewed in Ref. 35).

Although FH-protein-mediated localization of profilin during cytokinesis is likely to be important, there is also evidence that profilin regulates FH protein function. In *S. pombe*, profilin mutations abolish the localization of cdc12 to the actin ring[5], indicating that profilin is required either for the recruitment of cdc12 to the ring or for the stable association of cdc12 with the ring.

As with profilin, the relationship of Rho to FH protein function remains unclear. Since active Rho has numerous cellular effectors[35], it might regulate other cytoskeletal components while bound to an FH protein. It is known that Rho interacts with and stimulates a kinase that phosphorylates and thereby inhibits the myosin light-chain phosphatase (reviewed in Ref. 39). The net result is an increase in the formation of myosin II filaments and in the interaction of myosin II with actin. Interacting Rho and FH proteins could thus act in parallel to direct the localized organization or activity of an actin–myosin-based contractile apparatus.

The ability of Bni1p to interact with both profilin and another actin-binding protein (Bud6p/Aip3p) is reminiscent of proteins in the Ena/VASP (Enabled/vasodilator-stimulated phosphoprotein) family. These proteins play an active role in microfilament assembly and cell motility and, like FH proteins, have a proline-rich core[40]. Ena/VASP proteins interact with profilin, as well as with both zyxin and vinculin, and thus might have a function in cell motility analogous to that of FH proteins in cytokinesis.

In order for an FH-protein-associated actin cytoskeleton to mediate cell shape changes, it is necessary that the protein complex be anchored in some manner to specific sites along the plasma membrane. It is attractive to speculate that the FH2 domain participates in this tethering process. Whether or not this is true, the high degree of sequence conservation within the FH2 region is consistent with FH proteins interacting, through their FH2 domains, with at least

one class of molecules in addition to Rho, profilin and Bud6-type proteins.

Future directions

Despite a number of recent discoveries, much remains to be learned about FH proteins and their role in the molecular mechanisms governing changes in cell shape and polarity. In cytokinesis, the order of action of FH proteins relative to other components of the contractile ring is uncertain, nor is it known to what extent the role of FH proteins in this process is regulatory or structural. It is also unclear whether the vertebrate formins act in the same manner and in the same cellular milieu as other family members.

Further characterization of FH protein function might help shed light on the cellular coordination of microtubule and microfilament assembly and function. Results obtained in *S. pombe* suggest that FH proteins help mediate the process by which the microtubules that comprise the spindle apparatus direct the localized assembly of actin and myosin into a cleavage ring[5]. Similarly, in *D. melanogaster*, there is evidence that the CAPU protein acts at a functional interface between the tubulin- and actin-based cytoskeletons[2,8].

The finding that FH proteins participate in cell division in *S. cerevisiae* as well as in higher eukaryotes has added to the growing list of cytokinesis factors common to the cells of budding yeast and animals (see, for example, Ref. 41). At the same time, the discovery that mutations in a human FH protein result in deafness adds to the accumulating evidence that cytoskeletal abnormalities underlie a significant fraction of human hearing disorders. Investigations into FH protein function are therefore also likely to enrich our knowledge of a yeast cleavage process that, contrary to long-held opinions, might involve a contractile apparatus and of a human sensory process for which an active role of the cytoskeleton is well accepted but only poorly understood.

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New research institute in Dresden

January 1998 saw finalization of the plans for the new Max-Planck-Institute for Molecular Cell Biology and Genetics in Dresden, Germany. The overall aim of the institute is to assemble a broad-spectrum research community examining a wide range of cellular and molecular topics, leading towards a coherent view of cell organization during development and in adult organisms. There will also be a particular emphasis on integrating technological development into the research programme.

Construction of the new building will start soon, and it is currently planned that scientists will move into it in the year 2000. The institute is intended to house 400 staff in total, who will include the acting director, Kai Simons, and four other research directors, three of whom are Wieland Huttner, Anthony Hyman and Marino Zerial. There will be approximately 19 other group leaders, plus staff involved in technology development, and a strong programme for training postdoctoral researchers and students in modern cell and molecular biology techniques.

Further information about MPI Dresden can be obtained from Kai Simons, E-mail: dresden@embl-heidelberg.de