Leading Edge
Essay
Cell

The BAR Domain Superfamily: Membrane-Molding Macromolecules

Adam Frost,[1,3,4,7] Vinzenz M. Unger,[1,3,*] and Pietro De Camilli[2,3,4,5,6,*]
[1]Department of Molecular Biophysics & Biochemistry
[2]Departments of Cell Biology and Neurobiology
[3]Interdepartmental Neuroscience Program
[4]Howard Hughes Medical Institute
[5]Kavli Institute for Neuroscience
[6]Program in Cellular Neuroscience, Neurodegeneration & Repair
Yale University School of Medicine, New Haven, CT 06510, USA
[7]Present address: Department of Cellular and Molecular Pharmacology, University of California, San Francisco and California Institute for Quantitative Biosciences, San Francisco, CA 94158, USA
*Correspondence: vinzenz.unger@yale.edu (V.M.U.), pietro.decamilli@yale.edu (P.D.C.)
DOI 10.1016/j.cell.2009.04.010

Membrane-shaping proteins of the BAR domain superfamily are determinants of organelle biogenesis, membrane trafficking, cell division, and cell migration. An upsurge of research now reveals new principles of BAR domain-mediated membrane remodeling, enhancing our understanding of membrane curvature-mediated information processing.

Walls, fences, and barriers: these are the metaphors often used to describe the properties of cellular membranes. Yet, these "walls" are highly dynamic structures that can bend, split, and fuse as cells remodel their stunning variety of shapes and internal structures. To accomplish this feat, cells use proteins that are recruited from the cytosol to reversibly shape membranes into tunnels, bubbles, furrows, fingers, and feet. In cooperation with the cytoskeleton and with metabolic changes within the phospholipid bilayer, these membrane-shaping proteins fashion the reaction surfaces and compartments that enable organelle biogenesis, intracellular membrane trafficking, cell division, and cell migration. Moreover, mechanisms that control membrane morphology underlie cell-cell interactions and thus control development, infection, formation of syncytia, and immune responses. In this Essay, we discuss the membrane-shaping proteins of the BAR domain superfamily and how they mold membranes in cellular processes and organelles.

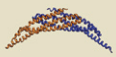
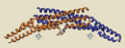
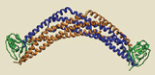
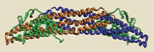
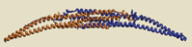
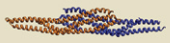
Prior to the discovery of their membrane-remodeling properties, BAR domains were identified as conserved modules shared by the yeast proteins Rvs161 and Rvs167 (reduced viability upon starvation) and the metazoan amphiphysin/BIN (bridging interactor) proteins (Takei et al., 1999; Farsad et al., 2001; Peter et al., 2004). Fifteen eukaryotic crystal structures from the superfamily have now been solved. Due to primary sequence divergence, the BAR domain crystal of human arfaptin-2 (Tarricone et al., 2001) was recognized as the founding BAR structure only after a second BAR crystal structure (of *Drosophila* amphiphysin) revealed homology between these domains (Peter et al., 2004). Together, the crystal structures demonstrate that the BAR domain superfamily is composed of subsets of unique families, including the "classical" BARs, the F-BARs (Fes/CIP4 homology-BAR), and the I-BARs (Inverse-BAR) (Frost et al., 2007; Table 1). Each of these families share the defining elements of a BAR domain: coiled-coils that dimerize into modules with a positively charged surface (Peter et al., 2004; Shimada et al., 2007).

A recent cryo-EM analysis of the F-BAR dimer found at the N terminus of Toca (Transducer of cdc42-dependent actin assembly) family proteins demonstrated how this module may associate with membranes to shape cylindrical tubules (Frost et al., 2008). By fitting atomic models of F-BAR dimers (Shimada et al., 2007) into cryo-EM reconstructions of membrane tubules, this study showed how clusters of cationic residues on the concave surface of the F-BAR module engage the membrane bilayer and enable rigid F-BAR dimers to impose their crescent shapes on the underlying membrane (Figure 1). Moreover, by visualizing F-BAR modules in a membrane-bound context, this work demonstrated that membrane tubule formation depends on the self-assembly of F-BAR modules into a helical coat (Figure 1). It will be crucial to determine how these observations reflect the general properties of the superfamily and to establish their relevance to in vivo events.

BAR domains may induce membrane curvature de novo (e.g., "induced fit"), stabilize curvature generated by other forces, or detect curvature in order to recruit cytosolic factors to membranes of a particular shape or size. Inducing and sensing curvature are not exclusive of one another: local deformations caused by BAR domain proteins will facilitate binding of additional BARs and thereby generate a positive-feedback cycle for curvature propagation. Computational studies reinforce the notion that BAR domains can induce both local membrane bending and anisotropic membrane remodeling over large distances (Ayton et al., 2007).

Distinctive features of individual BAR domain-containing proteins reveal unique adaptations, suggesting that BAR domains

Table 1. Human BAR Domain Superfamily Proteins

BAR Domains		Human BAR Domain Proteins	Disease Association
Classical BAR		Arfaptins, ICA69, PICK1, DNMBP (Tuba)	Alzheimer's disease (DNMBP), diabetes mellitus (ICA69)
N-BAR (N-terminal amphiphathic helix-BAR)		Amphiphysins/BINs, endophilins/BIFs, nadrins	Paraneoplastic stiff-person syndrome (amphiphysin-1), centronuclear myopathy (amphiphysin-2)
BAR-PH (BAR-Pleckstrin Homology)		Oligophrenins, APPLs, GRAFs, centaurin-βs	Mental retardation, epilepsy, and cerebellar hypoplasia syndrome (oligophrenin)
PX-BAR (PhoX-BAR)		Sorting nexins 1,2,5,6,9	
F-BAR (FCH-BAR, Fes/CIP4 Homology-BAR)		Toca-1, FBP17, CIP4 FCHo1, FCHo2, Fes/Fer kinases, syndapins, srGAPs, PSTPIP-1, PSTPIP-2	Pyogenic arthritis, pyoderma gangrenosum & acne syndrome (PSTPIP), 3p-syndrome (srGAP3)
I-BAR (Inverse-BAR; IMD-BAR, or IRSp53-MIM homology domain)		IRSp53, MIM, IRTKS	Bladder and prostate carcinoma (MIM), Tourette syndrome (IRSp53)

can be used in a variety of contexts for different functions (Frost et al., 2007; Table 1). For example, the presence of flanking phosphoinositide binding motifs (Lee et al., 2002) or phox (PX) or pleckstrin homology (PH) domains can help to direct BAR proteins to membranes enriched in cognate phosphoinositides. Alternatively, in endophilin and amphiphysin, BAR domains are conjoined with N-terminal sequences of ~26 residues that appear to fold into amphipathic α helices (so-called N-BAR domains) in the local environment of the bilayer polar-apolar interface. The intercalation of this helix into one leaflet of the bilayer may act like a "wedge" that causes local buckling when the polar headgroups of one lipid monolayer are pushed apart, or like an "anchor" that reduces the k_{off} for membrane binding (Farsad et al., 2001; Gallop et al., 2006). Though the sequence of events has not yet been determined, helix insertion may facilitate subsequent binding of the BAR module to enhance or further stabilize curvature. Unexpectedly, in some BAR domains a convex surface (rather than a concave surface) is the bilayer-binding interface. These "Inverse" or I-BAR domains promote inverse tubulation or the generation of filopodia-like extensions (Mattila et al., 2007).

Linking Membranes with the Cytoskeleton

Several members of the BAR domain superfamily provide a link between the membrane and the membrane-associated cytoskeleton. The nucleation of actin filaments at the plasma membrane generates mechanical forces that drive migrating cells, cell division, protrusions or invaginations of the membrane, the internalization of vesicles during endocytosis, and the "rocketing" of intracellular vesicles. F-actin polymerization is triggered by Rho-family GTPases and by the lipids PI(4,5)P_2 and PI(3,4,5)P_3, in coordination with nucleating factors such as the Wiskott-Aldrich syndrome protein (WASP) and the Wiskott-Aldrich verprolin (WAVE) protein (Takenawa and Suetsugu, 2007). Many BAR domain proteins are linked to actin nucleation by multiple mechanisms and may coordinate this process with membrane remodeling events. For example, some BAR proteins bind to and help to activate WASP/WAVE proteins. Furthermore, as these BAR proteins form dimers, they functionally dimerize the verprolin-cofilin-acidic (VCA) domains at the C termini of WASP/WAVE proteins. Dimerization of WASP/WAVE VCA domains appears to be a potent means of activating the Arp2/3 complex, which is involved in actin nucleation (Padrick et al., 2008). In addition, some BAR proteins act as effectors or regulators of Rho-family GTPases: they recruit the phosphoinositide phosphatase Synaptojanin, which regulates PI(4,5)P_2 and PI(3,4,5)P_3, and dynamin, whose role in membrane fission is interconnected with actin dynamics (Itoh and De Camilli, 2006; Takenawa and Suetsugu, 2007). Other BAR proteins bind to and "bundle" actin fibers directly (Takenawa and Suetsugu, 2007). A striking case of this multifunctionality is the protein Tuba (also called dynamin-binding protein), which has four N-terminal SH3 domains, a DH domain, a BAR domain, and two C-terminal SH3 domains. The four N-terminal SH3 domains have strong avidity for dynamin, the DH domain is a Cdc42 GEF, and the C-terminal SH3 domains bind directly to N-WASP and Ena/VASP proteins (Itoh and De Camilli, 2006).

Regulation by GTPases

The physical and functional relation to small GTPases, which together with phosphoinositides recruit cytosolic proteins to membrane compartments, seems to be important for the functions of BAR domain proteins. These GTPases coordinate interactions between BAR proteins, their target membranes, a variety of effector proteins, and actin filaments (Habermann, 2004). BAR domain proteins known to interact with small GTPases include arfaptin (an effector of Arf and a ligand for Rac) (Tarricone et al., 2001); IRSp53 (a Rac effector implicated in filopodia formation) (Miki et al., 2000); Toca-1, Toca-2/FBP17, and Toca-3/CIP4 (SH3-dependent WASP and dynamin recruitment plus HR1-dependent Cdc42 binding) (Ho et al., 2004; Itoh et al., 2005); APPL, a Rab5/21 effector that participates in growth factor receptor trafficking and signaling (Miaczynska et al., 2004); and nervous wreck, a synaptic protein that cooperates with Cdc42 on Rab11-

positive endosomes to facilitate WASP-mediated actin polymerization (Rodal et al., 2008). In fact, the BAR proteins IRSp53 and Arfaptin were initially characterized as binding partners for Rac GTPases (Miki et al., 2000; Tarricone et al., 2001). These observations hint at a fundamental regulatory network involving the interplay among BAR-mediated membrane deformation, the nucleation of actin fibers, and signaling through small GTPases.

Cellular Structures and BAR Proteins

Endocytic Tubules and Vesicles

Membrane budding to produce vesicles is a process that, by definition, implies the generation of membrane curvature. The morphological description of proteins that coat the cytoplasmic surface of vesicles and the subsequent molecular characterization of these vesicular "coats" through biochemical, genetic, and structural studies have given us insights into the mechanisms by which curvature of the membrane bilayer can be generated and stabilized. Tubular necks—often observed prior to the fission of coated vesicles from the donor membrane (Goldenthal et al., 1984)—were thought to result from physical forces pulling on coated buds in the absence of fission (Figure 1). The discovery of BAR domain proteins and the molecular characterization of dynamin and other curvature-generating factors showed how membrane-associated proteins or tubular coats can induce bud neck constriction and the formation of membrane tubules. BAR domain proteins are particularly important in endocytosis, where the generation of curvature is coupled tightly to reorganization of the actin cytoskeleton associated with the plasma membrane. For example, a subset of BAR proteins, including amphiphysin, endophilin and SNX9, may participate in clathrin-mediated endocytosis by acting as hubs of a protein network that coordinates bud neck constriction, actin assembly, and recruitment of downstream factors needed for fission and uncoating (Takei et al., 1999; Farsad et al., 2001; Yarar et al., 2007). The more shallow membrane curvature induced by F-BAR proteins (e.g., syndapin and Toca) may deform the bilayer early during curvature induction, although this remains to be tested (Shimada et al., 2007).

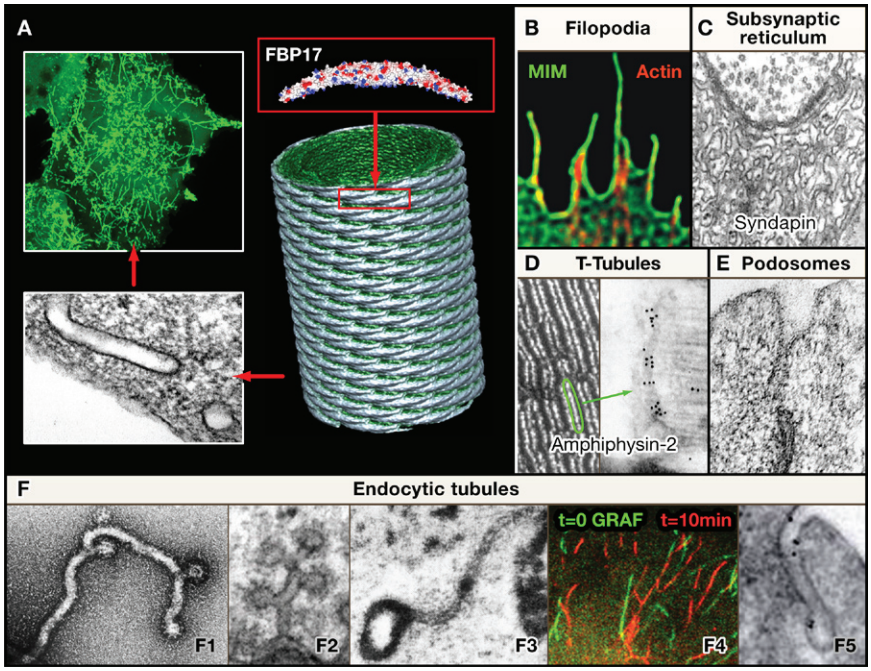


Figure 1. Cellular Structures and BAR Domain Proteins

(A) Plasma membrane tubules in cells demonstrating the shape-based scaffolding properties of the F-BAR structure. Cells expressing GFP-FBP17 visualized by fluorescence (top left), by transmission electron microscopy (TEM; bottom left), and by cryo-EM-derived single particle reconstruction of an F-BAR-coated tubule generated in vitro (bottom and top right) (Shimada et al., 2007, Frost et al., 2008).

(B) I-BAR domains of the missing-in-metastasis (MIM) protein localize to the plasma membrane and filopodia (Mattila et al., 2007; originally published in JCB *176*, 953–964).

(C) TEM of a *Drosophila* neuromuscular synapse engineered to overexpress syndapin in muscle, revealing an expansion of the subsynaptic reticulum (reprinted with permission from Kumar et al., 2009).

(D) (Left) Immunofluorescence of a skeletal muscle frozen section demonstrating muscle amphiphysin-2 (white) along transverse bands flanking the Z-line. (Right) Frozen section showing immunogold-labeled muscle amphiphysin-2 revealing its concentration on a T-tubule (Butler et al., 1997; originally published in JCB *137*,1355–1367).

(E) TEM of a transformed BHK21 cell cut perpendicular to the substratum to demonstrate the presence of tubular membrane invaginations in a podosome (Ochoa et al., 2000; originally published in JCB *150*, 377–389).

(F1) Negative staining of liposomes incubated with amphiphysin-1 and a clathrin coat fraction (reprinted with permission from Macmillan Publishers Ltd: Takei et al., Nat. Cell Biol. *1*, 33–39, 1999; copyright 1999). (F2) TEM of the synapse of a neuron deficient in dynamin-1, showing clathrin-coated endocytic pits originating from a plasma membrane tubular invagination ~30 nm in diameter (from Ferguson et al., 2007, Science *316*, 570–574; reprinted with permission from AAAS). (F3) TEM showing an endocytic coated pit with a narrow-neck connection to the surface (reprinted from Exp. Cell Res., Goldenthal et al., 1984, *152*, pp. 558–564, copyright 1984; with permission from Elsevier). (F4) GFP-GRAF1 endocytic tubules turn over in ~10 min (Lundmark et al., 2008). (F5) TEM of immunogold-labeled glycosyl phosphatidylinositol (GPI)-anchored proteins internalized via a putative clathrin- and dynamin-independent invagination (reprinted with permission from Macmillan Publishers Ltd: Mayor and Pagano, Nat. Rev. Mol. Cell Biol. *8*, 603–612, 2007; copyright 2007). The invagination is like that induced by GRAF1 (Lundmark et al., 2008).

In budding yeast, the BAR proteins Rvs161/167 play roles both in endocytosis and in the regulation of the actin cytoskeleton. Live-cell imaging demonstrates that the Rvs161/167 proteins are recruited to late-stage endocytic actin patches, and that in yeast lacking these proteins there is a retraction or "yo-yo" movement of the endocytic membranes generated at these sites after the initial internalization movement (Kaksonen et al., 2005). These observations support the notion that the Rvs proteins coordinately control actin fiber rearrangements, invagination of endocytic buds, and perhaps fission (as this organism appears to lack an endocytic dynamin). Moreover, BAR proteins may help to fashion the membrane-trafficking intermediates known as CLathrin-Independent Carriers (CLICs) or GPI-Enriched Endocytic

Compartments (GEECs) (Mayor and Pagano, 2007). For example, the BAR-PH and RhoGAP domain-containing protein GRAF1 participates in the clathrin-independent endocytosis of bacterial exotoxins and GPI-linked proteins (Lundmark et al., 2008).

Endosomes

Following fission from the plasma membrane, nascent vesicles are transported through a hierarchy of endosomal organelles that function as signaling and sorting stations. From endosomes, some material is rerouted back to the cell surface, whereas other material is either targeted to the trans-Golgi network or delivered to lysosomes for degradation. The endosome system comprises a population of morphologically and functionally heterogeneous organelles characterized by a growing list of unique lipid and protein components including BAR domain proteins such as APPL1/2 (Miaczynska et al., 2004) and the sorting nexins (Cullen, 2008). These proteins may assist in signaling and sorting processes by generating membrane microdomains or by segregating cargo into tubular extensions of these organelles. Some of the sorting nexins are components of the retromer, a protein complex that acts as a sorting coat on endosomes to mediate transport of trans-membrane cargo back to the trans-Golgi network via tubular transport intermediates (Bonifacino and Hurley, 2008). The formation of these tubular membranes is most likely attributable, at least in part, to the properties of the PX-BAR proteins SNX1, SNX2, SNX5, and SNX6. The PX-BAR module most likely drives tubule formation and may recruit the cargo recognition complex—composed of Vps26, Vps29, and Vps35—to coordinate cargo sorting with membrane tubule formation.

T-Tubules

T-tubules are narrow tubular invaginations of the plasma membrane that propagate electrical signals to the core of skeletal muscle cells and participate in excitation-contraction coupling. The presence of these tubules suggests an abundance of plasma membrane tubulating factors. Indeed, a splice variant of the BAR protein amphiphysin-2 is highly expressed in skeletal muscle and is localized on T-tubules (Lee et al., 2002). Interestingly, as T-tubules are not endocytic structures, this splice variant lacks binding sites for clathrin and the clathrin adaptor AP-2 and comprises instead a polybasic sequence (encoded by exon 10) that enhances its affinity for the plasma membrane (Lee et al., 2002). This protein, likely in cooperation with other proteins, plays a critical role in the induction and stabilization of this unique organelle. Genetic disruption of the only *amphiphysin* gene in *Drosophila* disrupts the T-tubule network (Razzaq et al., 2001), and missense mutations in the human gene encoding amphiphysin-2 cause myopathies (Nicot et al., 2007).

Podosomes

Podosomes are adhesion structures at contact sites between motile cells and their substrates. In contrast to focal adhesions, podosomes are highly dynamic structures that allow cells to translocate rapidly over surfaces and within tissues. They are also sites of extracellular matrix degradation and have been implicated in the migration of metastatic cancer cells (Ochoa et al., 2000). Podosomes are characterized by columnar arrays of actin arranged perpendicular to the attachment plane of the cell, which often contain a narrow tubular invagination of the plasma membrane throughout their length (Figure 1; Ochoa et al., 2000). Dynamin-2 and several proteins of the BAR superfamily are concentrated at these sites (Ochoa et al., 2000; P.D.C., unpublished data). Recently, amphiphysin-1 and dynamin-2 have been implicated in the formation of tubular structures reminiscent of podosomes at the junction between Sertoli cells and spermatids in mouse testis (Kusumi et al., 2007). The functions of podosome plasma membrane invaginations, including a potential endocytic function, remain to be determined.

Filopodia

One intriguing example of the interplay between BAR-mediated membrane deformation and the actin-based cytoskeleton is found in the formation of some types of filopodia induced by proteins with I-BAR domains (Mattila et al., 2007). I-BARs are found at the N termini of proteins like IRSp53 and MIM (missing-in-metastasis). The term "inverse" refers to the property of these domains to induce a curvature opposite to that produced by classical BAR domains—that is, protrusions of the plasma membrane rather than invaginations—through their convex and cationic surface (Saarikangas et al., 2009). Moreover, I-BAR proteins bind to Rac GTPases and to WAVE2 through SH3 domains and also bind to actin directly through WASP-homology 2 (WH2) domains (Takenawa and Suetsugu, 2007). Future efforts to visualize how I-BAR filopodia connect to actin filaments will advance our understanding of the mechanical properties and signaling outputs of these unique structures.

Mitochondria and Autophagosomes

Endophilin-B1/Bif-1 plays a role in the maintenance of mitochondrial morphology. Depletion of endophilin-B1 by RNA interference using short-hairpin RNAs leads to the dissociation of the outer mitochondrial membrane and to the formation of vesicular and tubular structures from the remnants of this membrane (Karbowski et al., 2004). These results phenocopy knockdown of the dynamin homolog Drp1 (dynamin-related protein 1), a protein implicated in mitochondrial fission. Thus, Drp1 and endophilin-B1 may act in concert, and perhaps may interact directly, in the maintenance of mitochondrial morphology (Karbowski et al., 2004). Such a partnership would be reminiscent of the SH3 domain-dynamin interactions that characterize the BAR proteins involved in endocytosis. Endophilin-B1 also may interact with Bax to promote apoptosis following cytokine withdrawal (Takahashi et al., 2005). The connection between endophilin-B1 and apoptosis is particularly intriguing as this protein also appears to play a role in autophagy (Takahashi et al., 2007). Cellular self-digestion through autophagy is recognized increasingly as fundamental to development, life-span extension, and cell death. Its dysfunction is thought to be implicated in neurodegenerative, cardiovascular, and neoplastic diseases. The process of autophagy involves the sequestration of cytosol and organelles into double-membrane vesicles (autophagosomes) that undergo a series of shape changes and subsequently fuse with lysosomes for cargo degradation. Though its mechanism of action remains elusive, endophilin-B1/Bif-1 was shown recently to be required for

the formation of autophagosomes (Takahashi et al., 2007). Regarding the potential dual link of endophilin-B1/Bif-1 to mitochondrial dynamics and to autophagy, mitochondrial Drp1-dependent fission may work together with autophagy to eliminate damaged mitochondrial proteins. Defects in this process may play a role in the neurodegeneration underlying Parkinson's disease (McBride, 2008).

Cleavage Furrows and Contractile Rings

The coordination between membrane deformation and the cytoskeleton is nowhere as dramatic as in the formation of the contractile actomyosin ring and the invagination of the plasma membrane during cell division. In fission yeast, a key participant in this elaborate process is the essential protein Cdc15. This protein is a founding member of the FCH (Fes-Cip4 homology) motif-containing family, and this sequence is now recognized as part of the F-BAR domain. Cdc15 was described originally as an SH3 domain-containing protein that regulates actin nucleation through recruitment of formins and type I myosins (Roberts-Galbraith and Gould, 2008). Cdc15 appears to act upstream of actomyosin ring polymerization prior to cell division and localizes with precursors of the contractile ring and fully formed contractile rings throughout cytokinesis (Wu et al., 2006; Figure 2). Based on the expectation that F-BAR proteins bind to the plasma membrane, Cdc15 may couple the actomyosin ring directly to the membrane while inducing or stabilizing the high degree of curvature observed at the cleavage furrow in fission yeast (Figure 2). Perhaps BAR proteins regulate the contractile apparatus during constriction by "sensing" the degree of curvature in the cleavage furrow. Alternatively, Cdc15-like proteins may initiate contractile ring formation by bending the membrane inward; other curvature-sensing proteins may detect or stabilize the still higher degree of curvature found at the point of maximum constriction in order to trigger disassembly of the contractile ring.

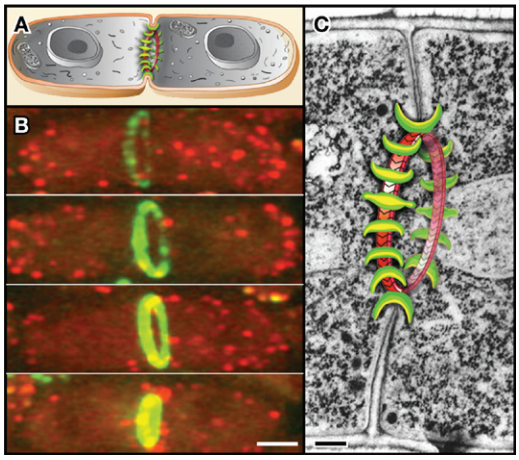


Figure 2. Do BAR Domain Proteins Link the Contractile Ring to the Cleavage Furrow?

(A) Shown is a cartoon of a dividing fission yeast cell with representations of where the F-BAR domains of Cdc15 (green) may localize in relation to the actomyosin contractile ring (red).

(B) Cells expressing mCFP-Wsp1 (red) and Cdc15-mYFP (green), showing that Cdc15p colocalizes with precursors of the contractile ring and with fully formed contractile rings at various stages of constriction (Wu et al., 2006; originally published in JCB *174*, 391–402).

(C) TEM of cleavage furrow invagination in fission yeast (reproduced with permission from Kanbe, 1989). The diameter of the edge of the invagination ranges from 50 to 80 nm, within the range of known BAR and F-BAR structures. Regions where F-BAR domains of Cdc15 may localize in relation to the contractile ring are shown.

Bar: 2000 nm (B), 100 nm (C).

Cdc15 and other BAR proteins are also found at actin patches—known sites of clathrin-mediated endocytosis in yeast—though Cdc15 only concentrates in actin patches at the cell tips during interphase (Wu et al., 2006; reviewed in Roberts-Galbraith and Gould, 2008). During mitosis, Cdc15 is dephosphorylated and moves exclusively from cell tips to the precursors of the contractile ring, before becoming an integral component of the fully formed ring (Figure 2). During constriction of the ring and ingression of the cleavage furrow, re-phosphorylated Cdc15 starts moving to newly formed actin patches adjacent to the cleavage furrow (that is, at the tips of the future daughter cells). Thus, a key question that needs to be addressed is whether the localization of BAR and F-BAR proteins at sites of cell division also reflects the need for ongoing endocytosis within or near the cleavage furrow.

In budding yeast and mammalian cells, the degree of membrane curvature found at the division site is dramatically different from the high degree of curvature seen in fission yeast (Figure 2). Yet there is evidence that even in these cells, BAR proteins play key roles during cytokinesis. The budding yeast homolog of Cdc15 (Hof1/Cyk2) is a known cytokinesis factor that forms a ring around the bud neck (Lippincott and Li, 1998). In addition, a recent study of the *S. cerevisiae* interactome suggests that Syp1—predicted to have a Cdc15-like F-BAR domain (Roberts-Galbraith and Gould, 2008)—is the hub of a network connecting WASP (Las17), the bud-neck septins (SHS1 and Cdc11), a myosin (Myo5), and the cytokinesis protein Mid2 (an anillin ortholog) as well as components of actin patches (Tarassov et al., 2008). Finally, the human protein PSTPIP1 possesses F-BAR and SH3 domains that are highly homologous with those of Cdc15 and localizes to the cleavage furrow of cultured human cells (Spencer et al., 1997). Together, these observations hint at the existence of an ancient but poorly understood circuit linking BAR domain superfamily proteins with cytokinesis in general and with the assembly, constriction, and disassembly of the contractile ring in particular.

Conclusions

The membrane-molding proteins of the BAR domain superfamily create a multiplicity of membranous structures whose forms underlie the function of many cellular processes. As fundamental determinants of membrane and cytoskeleton remodeling, proteins of the BAR domain superfamily will continue to be rich objects of inquiry. Their study has revealed new principles of membrane remodeling and contributed to establishing the concept of membrane curvature-mediated signaling. Challenging next steps will be to visualize and quantify their associations with membranes and cytoskeletal structures in living cells. Moreover, we have much to learn about their polymerization properties and the mechanisms by which cells regulate their nucleation and disassembly. It is hoped that further inquiry will yield novel insights into the growing number of diseases that result from BAR protein dysfunction and may point to new therapeutic strategies for the treatment of these conditions.

REFERENCES

Ayton, G.S., Blood, P.D., and Voth, G.A. (2007). Biophys. J. *92*, 3595–3602.

Bonifacino, J.S., and Hurley, J.H. (2008). Curr. Opin. Cell Biol. *20*, 427–436.

Butler, M.H., David, C., Ochoa, G.C., Freyberg, Z., Daniell, L., Grabs, D., Cremona, O., and De Camilli, P. (1997). J. Cell Biol. *137*, 1355–1367.

Cullen, P.J. (2008). Nat. Rev. Mol. Cell Biol. *9*, 574–582.

Farsad, K., Ringstad, N., Takei, K., Floyd, S.R., Rose, K., and De Camilli, P. (2001). J. Cell Biol. *155*, 193–200.

Ferguson, S.M., Brasnjo, G., Hayashi, M., Wolfel, M., Collesi, C., Giovedi, S., Raimondi, A., Gong, L., Ariel, P., Paradise, S., et al. (2007). Science *316*, 570–574.

Frost, A., De Camilli, P., and Unger, V.M. (2007). Structure *15*, 751–752.

Frost, A., Perera, R., Roux, A., Spasov, K., Destaing, O., Egelman, E.H., De Camilli, P., and Unger, V.M. (2008). Cell *132*, 807–817.

Gallop, J.L., Jao, C.C., Kent, H.M., Butler, P.J., Evans, P.R., Langen, R., and McMahon, H.T. (2006). EMBO J. *25*, 2898–2910.

Goldenthal, K., Pastan, I., and Willingham, M. (1984). Exp. Cell Res. *152*, 558–564.

Habermann, B. (2004). EMBO Rep. *5*, 250–255.

Ho, H.Y., Rohatgi, R., Lebensohn, A.M., Le, M., Li, J., Gygi, S.P., and Kirschner, M.W. (2004). Cell *118*, 203–216.

Itoh, T., and De Camilli, P. (2006). Biochim. Biophys. Acta *1761*, 897–912.

Itoh, T., Erdmann, K., Roux, A., Habermann, B., Werner, H., and De Camilli, P. (2005). Dev. Cell *9*, 791–804.

Kaksonen, M., Toret, C.P., and Drubin, D.G. (2005). Cell *123*, 305–320.

Kanbe, T. (1989). J. Cell Sci. *94*, 647–656.

Karbowski, M., Jeong, S.-Y., and Youle, R.J. (2004). J. Cell Biol. *166*, 1027–1039.

Kumar V., Fricke R., Bhar D., Reddy-Alla, S., Krishnan K.S., Bogdan, S., and Ramaswami, M. (2009). Mol. Biol. Cell. Published online February 25, 2009. 10.1091/mbc.E08-10-1072.

Kusumi, N., Watanabe, M., Yamada, H., Li, S.-A., Kashiwakura, Y., Matsukawa, T., Nagai, A., Nasu, Y., Kumon, H., and Takei, K. (2007). Cell Struct. Funct. *32*, 101–113.

Lee, E., Marcucci, M., Daniell, L., Pypaert, M., Weisz, O.A., Ochoa, G.C., Farsad, K., Wenk, M.R., and De Camilli, P. (2002). Science *297*, 1193–1196.

Lippincott, J., and Li, R. (1998). J. Cell Biol. *143*, 1947–1960.

Lundmark, R., Doherty, G.J., Howes, M.T., Cortese, K., Vallis, Y., Parton, R.G., and McMahon, H.T. (2008). Curr. Biol. *18*, 1802–1808.

Mattila, P.K., Pykalainen, A., Saarikangas, J., Paavilainen, V.O., Vihinen, H., Jokitalo, E., and Lappalainen, P. (2007). J. Cell Biol. *176*, 953–964.

Mayor, S., and Pagano, R. (2007). Nat. Rev. Mol. Cell Biol. *8*, 603.

McBride, H.M. (2008). J. Cell Biol. *183*, 757–759.

Miaczynska, M., Christoforidis, S., Giner, A., Shevchenko, A., Uttenweiler-Joseph, S., Habermann, B., Wilm, M., Parton, R.G., and Zerial, M. (2004). Cell *116*, 445–456.

Miki, H., Yamaguchi, H., Suetsugu, S., and Takenawa, T. (2000). Nature *408*, 732–735.

Nicot, A.S., Toussaint, A., Tosch, V., Kretz, C., Wallgren-Pettersson, C., Iwarsson, E., Kingston, H., Garnier, J.M., Biancalana, V., Oldfors, A., et al. (2007). Nat. Genet. *39*, 1134–1139.

Ochoa, G.C., Slepnev, V.I., Neff, L., Ringstad, N., Takei, K., Daniell, L., Kim, W., Cao, H., McNiven, M., Baron, R., and De Camilli, P. (2000). J. Cell Biol. *150*, 377–389.

Padrick, S.B., Cheng, H.C., Ismail, A.M., Panchal, S.C., Doolittle, L.K., Kim, S., Skehan, B.M., Umetani, J., Brautigam, C.A., Leong, J.M., and Rosen, M.K. (2008). Mol. Cell *32*, 426–438.

Peter, B.J., Kent, H.M., Mills, I.G., Vallis, Y., Butler, P.J., Evans, P.R., and McMahon, H.T. (2004). Science *303*, 495–499.

Razzaq, A., Robinson, I.M., McMahon, H.T., Skepper, J.N., Su, Y., Zelhof, A.C., Jackson, A.P., Gay, N.J., and O'Kane, C.J. (2001). Genes Dev. *15*, 2967–2979.

Roberts-Galbraith, R.H., and Gould, K.L. (2008). F-BAR Domain Proteins in Schizosaccharomyces pombe. In The Pombe Cdc15 Homology Proteins (Austin, TX: Landes Biosciences). http://www.landesbioscience.com/curie/chapter/3918/.

Rodal, A.A., Motola-Barnes, R.N., and Littleton, J.T. (2008). J. Neurosci. *28*, 8316–8325.

Saarikangas, J., Zhao, H., Pykalainen, A., Laurinmaki, P., Mattila, P.K., Kinnunen, P.K., Butcher, S.J., and Lappalainen, P. (2009). Curr. Biol. *19*, 95–107.

Spencer, S., Dowbenko, D., Cheng, J., Li, W., Brush, J., Utzig, S., Simanis, V., and Lasky, L.A. (1997). J. Cell Biol. *138*, 845–860.

Shimada, A., Niwa, H., Tsujita, K., Suetsugu, S., Nitta, K., Hanawa-Suetsugu, K., Akasaka, R., Nishino, Y., Toyama, M., Chen, L., et al. (2007). Cell *129*, 761–772.

Takahashi, Y., Karbowski, M., Yamaguchi, H., Kazi, A., Wu, J., Sebti, S.M., Youle, R.J., and Wang, H.-G. (2005). Mol. Cell. Biol. *25*, 9369–9382.

Takahashi, Y., Coppola, D., Matsushita, N., Cualing, H.D., Sun, M., Sato, Y., Liang, C., Jung, J.U., Cheng, J.Q., Mul, J.J., et al. (2007). Nat. Cell Biol. *9*, 1142–1151.

Takei, K., Slepnev, V.I., Haucke, V., and De Camilli, P. (1999). Nat. Cell Biol. *1*, 33–39.

Takenawa, T., and Suetsugu, S. (2007). Nat. Rev. Mol. Cell Biol. *8*, 37–48.

Tarassov, K., Messier, V., Landry, C., Radinovic, S., Molina, M., Shames, I., Malitskaya, Y., Vogel, J., Bussey, H., and Michnick, S. (2008). Science *320*, 1465.

Tarricone, C., Xiao, B., Justin, N., Walker, P.A., Rittinger, K., Gamblin, S.J., and Smerdon, S.J. (2001). Nature *411*, 215–219.

Wu, J.-Q., Sirotkin, V., Kovar, D.R., Lord, M., Beltzner, C.C., Kuhn, J.R., and Pollard, T.D. (2006). J. Cell Biol. *174*, 391–402.

Yarar, D., Waterman-Storer, C.M., and Schmid, S.L. (2007). Dev. Cell *13*, 43–56.