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REVIEW

BAR domain proteins—a linkage between cellular membranes, signaling pathways, and the actin cytoskeleton

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Abstract

Actin filament assembly typically occurs in association with cellular membranes. A large number of proteins sit at the interface between actin networks and membranes, playing diverse roles such as initiation of actin polymerization, modulation of membrane curvature, and signaling. Bin/Amphiphysin/Rvs (BAR) domain proteins have been implicated in all of these functions. The BAR domain family of proteins comprises a diverse group of multi-functional effectors, characterized by their modular architecture. In addition to the membrane-curvature sensing/inducing BAR domain module, which also mediates antiparallel dimerization, most contain auxiliary domains implicated in protein-protein and/or protein-membrane interactions, including SH3, PX, PH, RhoGEF, and RhoGAP domains. The shape of the BAR domain itself varies, resulting in three major subfamilies: the classical crescent-shaped BAR, the more extended and less curved F-BAR, and the inverse curvature I-BAR subfamilies. Most members of this family have been implicated in cellular functions that require dynamic remodeling of the actin cytoskeleton, such as endocytosis, organelle trafficking, cell motility, and T-tubule biogenesis in muscle cells. Here, we review the structure and function of mammalian BAR domain proteins and the many ways in which they are interconnected with the actin cytoskeleton.

Keywords BAR domain · Actin cytoskeleton · Membrane remodeling · Rho GTPases · Signaling

Introduction

BAR domain proteins were named after the founding members of this family: mammalian *B*in1 (Sakamuro et al. 1996) and *A*mphiphysin (Lichte et al. 1992), and yeast *R*vs167 (Sivadon et al. 1995), which were independently characterized and found to be related in sequence (Sakamuro et al. 1996). Generally, however, BAR domain proteins are unrelated at the sequence level. Membership into this family is strictly based on the presence of the BAR domain, which crystal structures revealed consists of a helical bundle of ~200–280 amino acids that associates in antiparallel fashion to form dimers of varying size and curvature (Habermann 2004; Millard et al. 2005; Peter et al. 2004; Tarricone et al. 2001), and the finding that this domain is also responsible for membrane binding and curvature sensing/generation in vitro and in cells (Farsad et al. 2001; Henne et al. 2007; Itoh et al. 2005; Mattila et al. 2007; Shimada et al. 2007; Takei et al. 1999; Tsujita et al. 2006). The link between BAR domain proteins and the cytoskeleton emerged almost immediately, as it was recognized that the actin cytoskeleton and budding pattern of yeast Rvs167 mutant cells was altered (Sivadon et al. 1995). It is now recognized that most functions associated with BAR domain proteins are also intimately linked to actin cytoskeleton remodeling, in processes such as endocytosis, organelle trafficking, cell motility, and T-tubule biogenesis in muscle cells (Antonny et al. 2016; Kessels and Qualmann 2015; Saarikangas et al. 2010; Scita et al. 2008; Suetsugu and Gautreau 2012; Zhao et al. 2011). Most BAR domain proteins contain additional domains that often participate along with the BAR domain in membrane binding and in protein-protein interactions. Among these so-called auxiliary domains, the most common is the Src homology 3 (SH3) domain that in many BAR domain proteins binds directly to cytoskeletal assembly factors and/or dynamin. Also abundant

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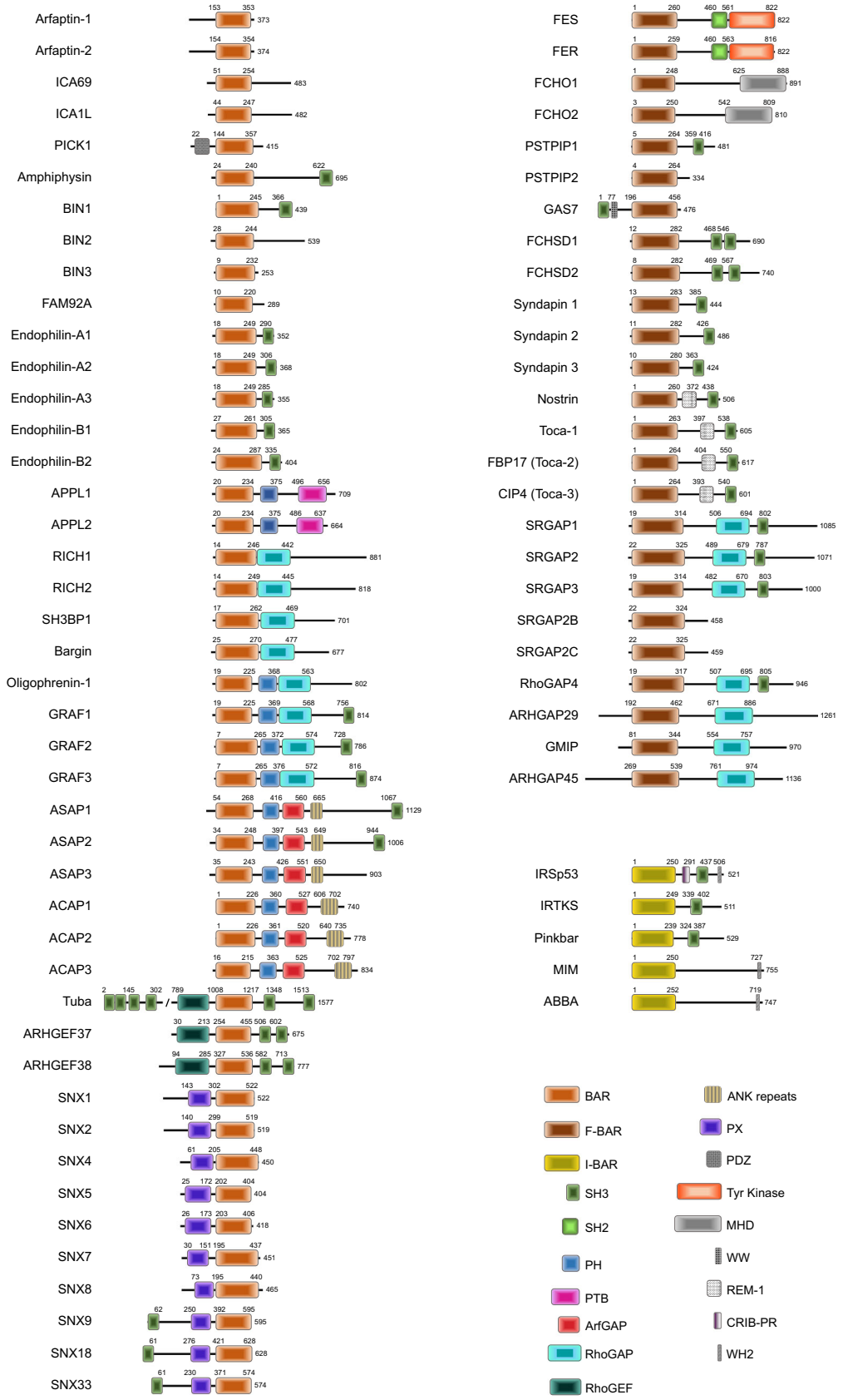


Fig. 1 Domain organization of BAR domain proteins. The classical crescent-shaped BAR subfamily is shown on the left and the F-BAR and I-BAR subfamilies are shown on the right (top and bottom, respectively). Protein domains are represented according to the domain key shown at the bottom right. The amino acid boundaries of domains are indicated (see also Supplementary Table 1)

among these proteins are domains that either recruit or regulate Rho-family GTPases, which are master regulators of the actin cytoskeleton (Hall 2012; Ridley 2015). Another common theme among BAR domain proteins is the presence of autoinhibitory intramolecular interactions, which are relieved by binding to other proteins and/or membranes. Here, we review these topics, with a particular emphasis on mammalian BAR domain proteins.

BAR domain structure, subfamilies, and membrane binding

BAR domain proteins interact with membranes mainly via non-specific electrostatic interactions (Saarikangas et al. 2010), and most share the ability to tubulate membranes in vitro and in cells (Farsad et al. 2001; Henne et al. 2007; Itoh et al. 2005; Mattila et al. 2007; Peter et al. 2004; Shimada et al. 2007; Takei et al. 1999; Tsujita et al. 2006). However, there is substantial variability in the type of membrane curvature BAR domain proteins generate. These differences emanate from two main factors: variability in the BAR domain fold itself and differences in the type of coats (or lattices) BAR domain proteins can form on membranes via BAR-BAR interactions.

Based on crystal structures, three major subfamilies of BAR domain proteins have been defined (Figs. 1 and 2 and Table S1): the classical crescent-shaped BAR (Peter et al. 2004; Tarricone et al. 2001), the more extended and less curved *F*es/CIP4 homology-BAR (F-BAR) (Frost et al. 2007; Henne et al. 2007; Itoh et al. 2005; Shimada et al. 2007), and the *I*nverse-BAR (I-BAR) subfamilies (Lee et al. 2007; Millard et al. 2005). While members of the I-BAR subfamily are more closely related to one another, there is substantial variability among members of both the BAR and F-BAR subfamilies, such that sequence or even structural alignments of these two subfamilies have been restricted to small subgroups of proteins. Here, we separately superimposed all the crystal structures of members of the three subfamilies based on the core antiparallel dimerization region, i.e., avoiding the distal ends of the dimers which diverge the most (Fig. 3). Based on this structural superimposition, we generated sequence alignments that were then extended to include

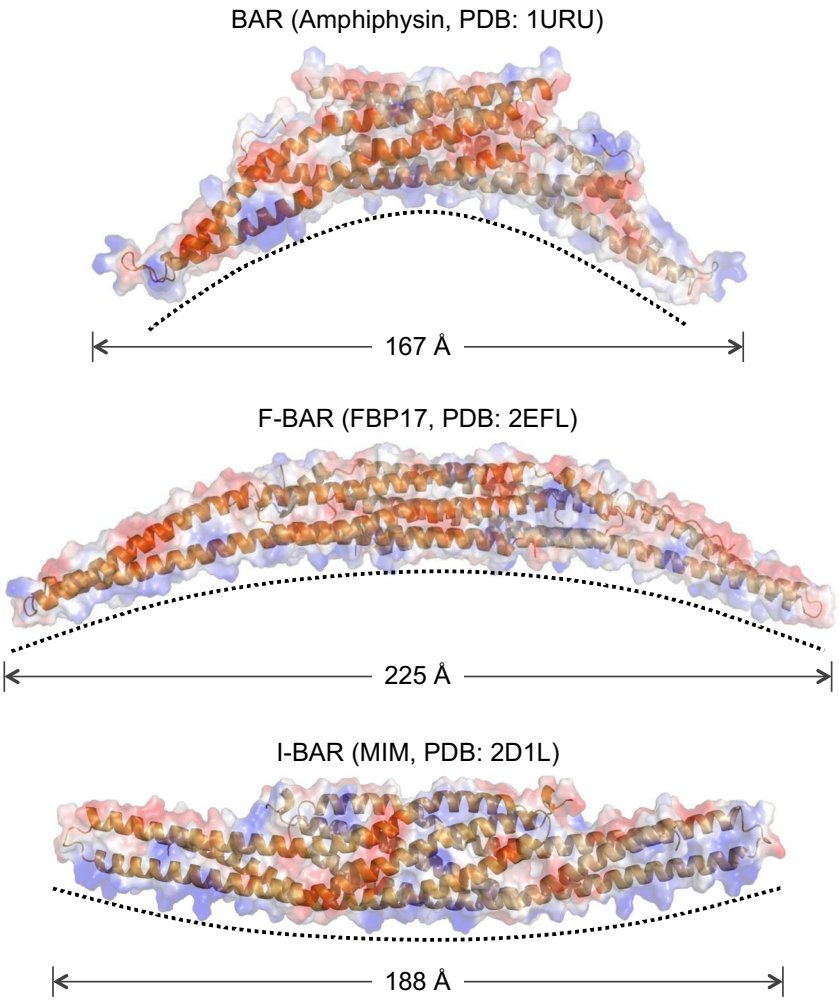


Fig. 2 Structures of representative members of the three major BAR domain subfamilies (as indicated). The figure also shows electrostatic surface representations, indicating the potential membrane-binding surfaces (dotted lines) and the overall dimensions of the dimers

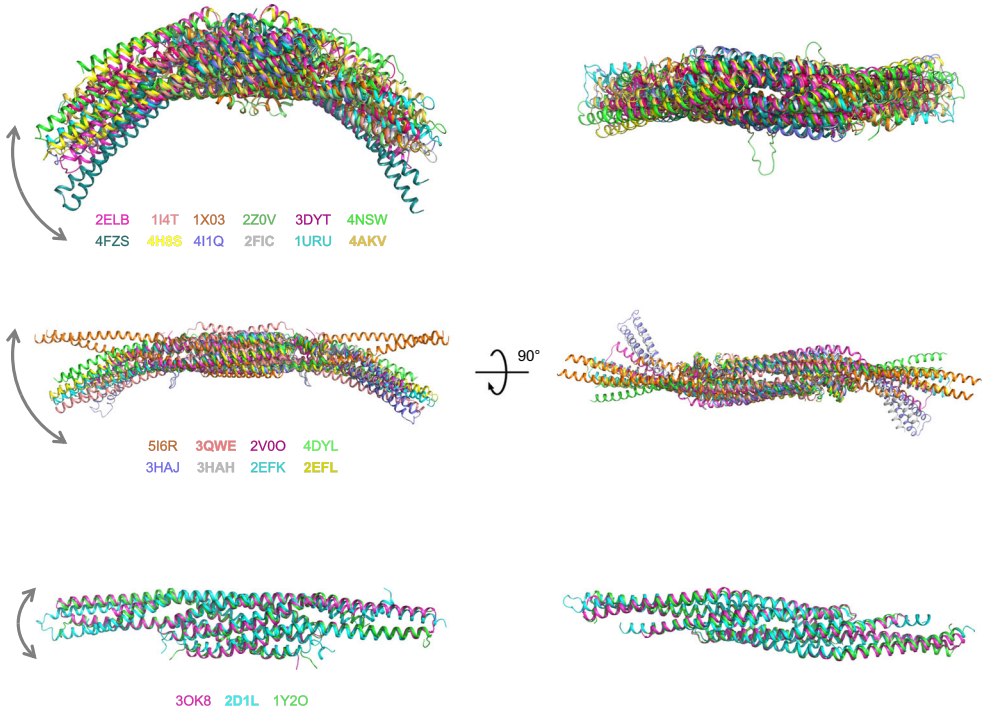
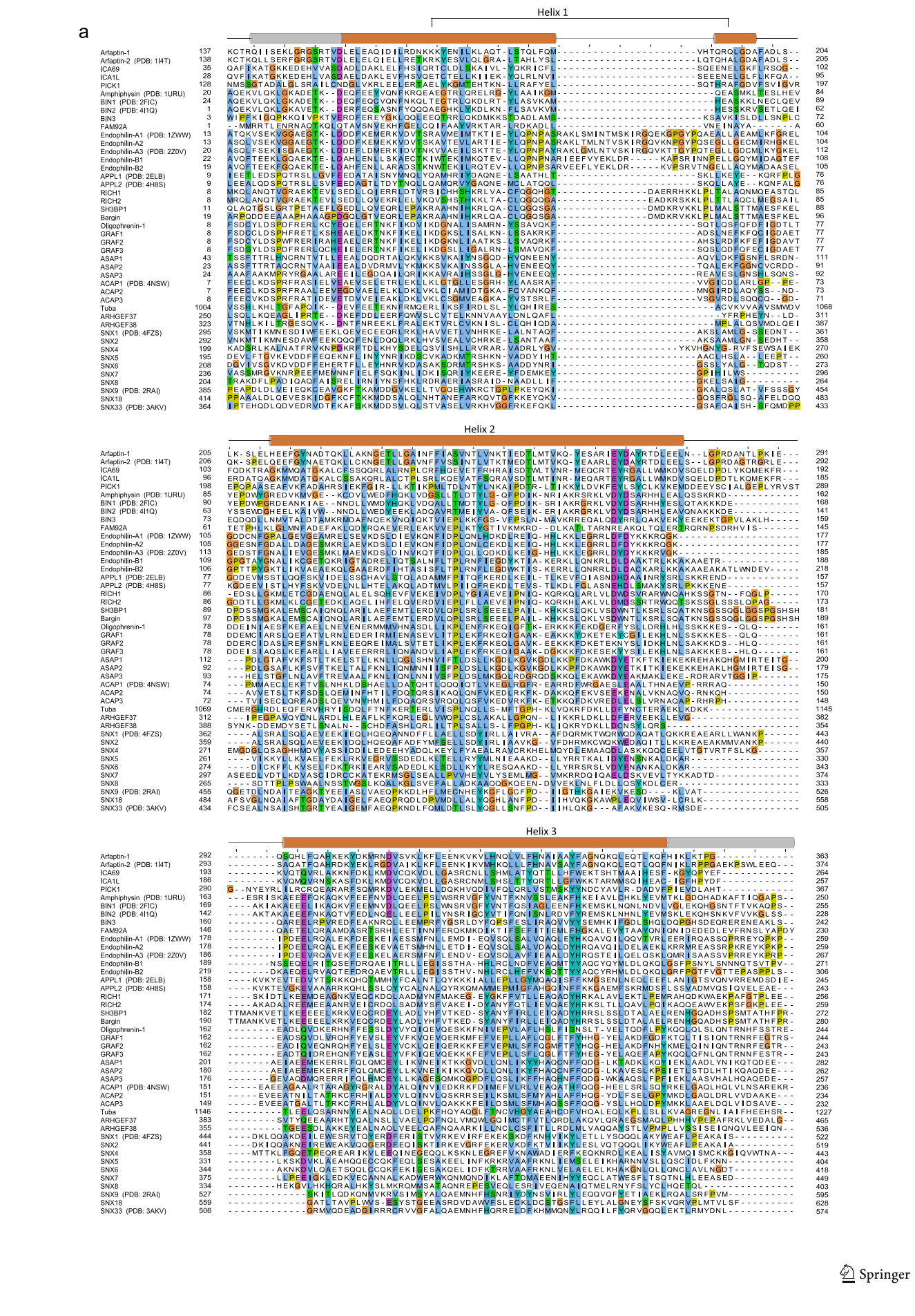


Fig. 3 Superimposition of the existing structures of members of the three BAR domain subfamilies. Two perpendicular views of the BAR domain portion (amino acids outside the BAR domain were removed when present) of the first-determined structure is shown for each protein (PDB codes are indicated, color coded). The structures were superimposed based on the core antiparallel dimerization region, i.e., avoiding the distal ends of the dimers which diverge the most, and using the program SALIGN (Braberg et al. 2012). However, some of the most divergent structures had to be manually superimposed using the PyMol Molecular Graphics System, Version 2.0 (Schrödinger, LLC). Curved arrows indicate the significant spread among structures at the distal ends of the dimers, which correlates with the membrane deformation capacity of each protein

other members of the subfamilies for which crystal structures have not yet been determined (Fig. 4). Such structural and sequence alignments highlight both common and distinctive features among BAR domain proteins. Thus, the basic folding unit of the BAR domain in all three subfamilies consists of three long and kinked α-helices, running antiparallel to one another. Two such units associate in antiparallel fashion through a "hand-shake" type of interaction to form a six-helix bundle with two-fold symmetry around the dimer interface, consisting mainly of hydrophobic interactions. Independent of the subfamily, BAR domain dimers are generally elongated and curved, and have a positively charged surface that mediates the interactions with negative charges of the membrane (Fig. 2). The main structural differences both among and within subfamilies emerge from the remarkable variability in the degree of bending and twisting that the three primary helices can exhibit, as well as variability in the angle of dimerization. Moreover, in several BAR domains, the primary helices are split or interrupted, and helical appendages and N- or C-terminal helical extensions to the core BAR domain are also often observed (Fig. 4). One notable example of such extensions is the so-called N-BAR fold, first described for Amphiphysin (Peter et al. 2004), which constitutes a variation of the classical BAR domain in which an amphipathic α-helix preceding the BAR domain inserts into the membrane and participates in membrane curvature generation. Another example is observed in the structure of Endophilin, in which the first helix (helix-1) of the BAR domain is interrupted by a ~20 amino acid insertion that folds partially into an extra amphipathic α-helix exposed on the membrane-binding, concave face of the BAR domain, and which functions as a wedge that penetrates the membrane for curvature generation (Gallop et al. 2006; Masuda et al. 2006; Weissenhorn 2005). Of note, Endophilin as well as RICH1 (Nadrin) also present an N-BAR helix like Amphiphysin (Bhatia et al. 2009; Gallop et al.

Fig. 4 Alignment of the sequences of all the members of the three BAR domain subfamilies. **a**–**c** BAR, F-BAR, and I-BAR subfamilies, respectively. The sequences are shown in the same order as the domain diagrams of Fig. 1. A subset of the sequences was first aligned based on the structural alignment shown in Fig. 3, and this initial alignment was then extended to include the sequences of proteins for which the structures are still unknown, using the program PROMALS3D (Pei and Grishin 2014). Further edition and display optimization of this alignment was performed with the program Jalview (Waterhouse et al. 2009). The three main helices of the BAR domain are indicated by the diagram shown on top of the alignments, where the gray-colored regions represent extensions to the three main helices of the BAR domain. For of each column, the background is colored according to residue type and conservation, using the Clustal X color scheme of Jalview: blue, conserved hydrophobic; red, conserved positively charged; magenta, conserved negatively charged; green, conserved polar; orange, conserved glycine; yellow, conserved proline; cyan, conserved aromatic; white, non-conserved


a
Helix 1
Helix 2
Helix 3
Arfaptin-1
Arfaptin-2 (PDB: 1I4T)
ICA69
ICA1L
PICK1
Amphiphysin (PDB: 1URU)
BIN1 (PDB: 2FIC)
BIN2 (PDB: 4I1Q)
BIN3
FAM92A
Endophilin-A1 (PDB: 1ZWW)
Endophilin-A2
Endophilin-A3 (PDB: 2Z0V)
Endophilin-B1
Endophilin-B2
SH3BP1
Bargin
Oligophrenin-1
GRAF1
GRAF2
GRAF3
ASAP1
ASAP2
ASAP3
ACAP1 (PDB: 4NSW)
ACAP2
ACAP3
Tuba
ARHGEF37
ARHGEF38
SNX1 (PDB: 4FZS)
SNX2
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SNX6
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SNX9 (PDB: 2RAI)
SNX18
SNX33 (PDB: 3AKV)

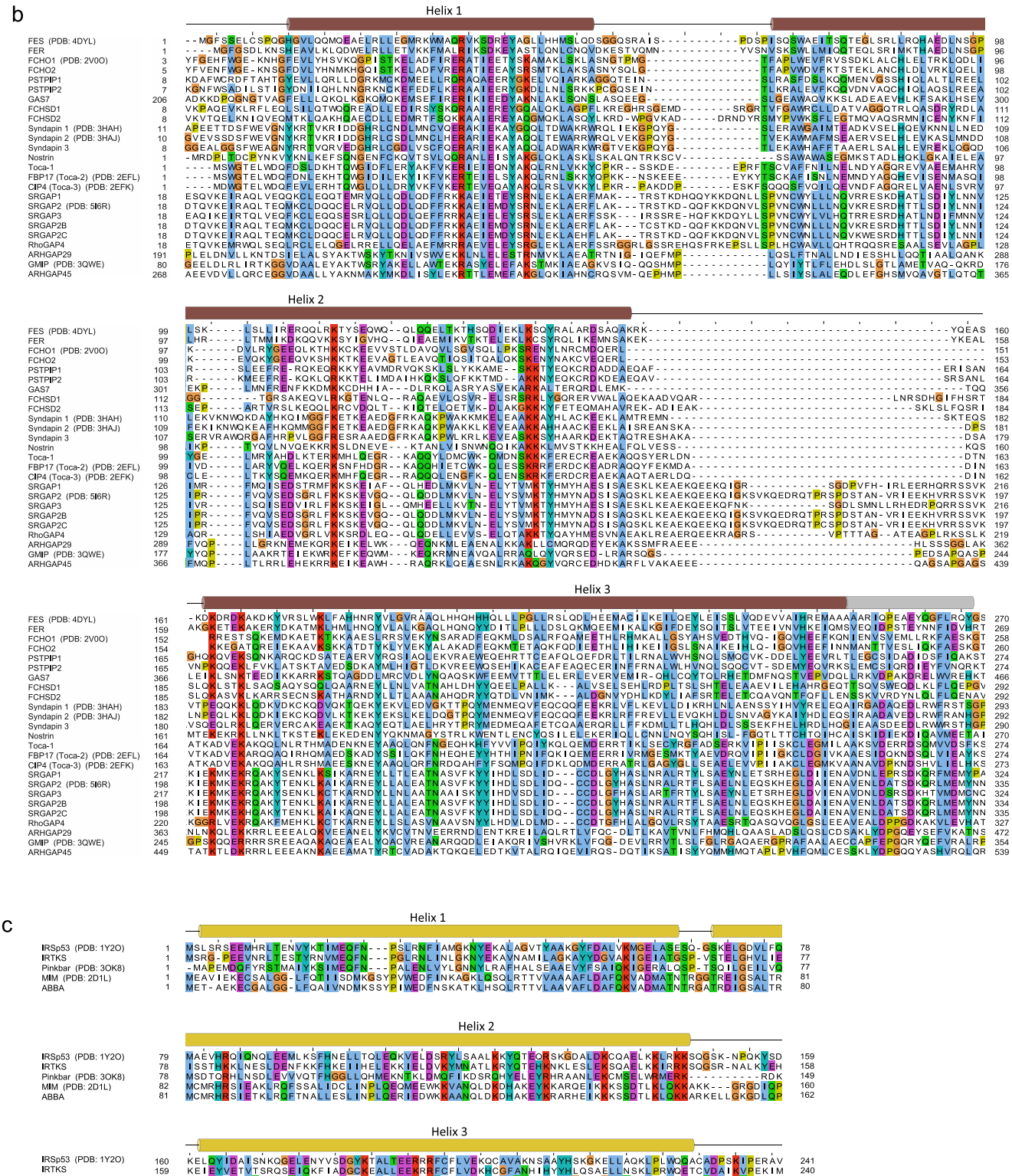

Fig. 4 continued.

2006). A similar insert, called the wedge loop, is observed on the membrane-binding face of the F-BAR domain protein Syndapin (Wang et al. 2009). The presence of additional membrane insertion motifs is now also documented in the I-BAR subfamily, in which at least two of the members, MIM and ABBA, insert an amphipathic helix into the membrane

bilayer that contributes to the larger diameter of the tubular structures formed by these two proteins in vitro and their more efficient filopodia formation in cells (Saarikangas et al. 2009).

The structural differences among BAR domain subfamilies correlate with important differences in the way they interact with cellular membranes, since to a large degree the BAR domain is thought to impose its shape on the membrane substrate through a so-called scaffolding mechanism (Blood et al. 2008; McMahon and Gallop 2005; Mim and Unger 2012; Zimmerberg and Kozlov 2006). Thus, the classical BAR domain is generally more curved and significantly shorter (~ 167 Å) than the F-BAR domain (~225 Å), which also has a shallower curvature (Fig. 2). However, both domains display significant variability in the degree of curvature. Among members of the BAR domain subfamily, SNX1 has the most highly curved structure visualized thus far (PDB: 4FZS, unpublished), whereas SNX9 has a rather flat structure (Pylypenko et al. 2007). The same is true of the F-BAR domain, displaying a nearly flat structure for SRGAP2 (Sporny et al. 2017), a curved structure for GMIP (PDB: 3QWE) and an S-shaped structure for Syndapin (also called PACSIN) (Rao et al. 2010; Wang et al. 2009). Regardless of these differences, the positively charged, membrane-binding surface in both the BAR and F-BAR domains is located on the concave face of the dimer, and accordingly, they generate positive membrane curvature by binding on the surface of tubular liposomes (Frost et al. 2008; Mim et al. 2012; Shimada et al. 2007). As a consequence of their larger size and shallower curvature, F-BAR domain proteins tend to generate membrane tubules of larger diameter than BAR domain proteins both in vitro and in cells (Frost et al. 2008; Henne et al. 2007; Itoh et al. 2005; Mim et al. 2012; Shimada et al. 2007). The I-BAR domain is intermediate in size (~ 188 Å) and has opposite curvature to that of the BAR and F-BAR domains, displaying a convex membrane-binding surface (Lee et al. 2007; Millard et al. 2005). Accordingly, the I-BAR domain binds to the inner leaflet of membrane tubules and generates negative membrane curvature, thus playing a role in the formation of cellular protrusions such as filopodia (Mattila et al. 2007; Saarikangas et al. 2009; Zhao et al. 2011). One exception is the I-BAR protein Pinkbar (*p*lanar *in*testinal- and *k*idney-specific *BAR* domain protein), which is specifically expressed in epithelial cells and has a nearly flat membrane-binding surface, such that it does not induce membrane tubulation but rather promotes the formation of planar membrane sheets (Pykalainen et al. 2011).

It is now clear that in addition to the structure of the BAR domain, other factors determine the way in which these proteins interact with and remodel cellular membranes. Most notable among these factors is the seemingly diverse ways in which BAR domains can interact with each other to form coats on membranes (Frost et al. 2008; McDonald and Gould 2016; Mim et al. 2012; Mim and Unger 2012; Shimada et al. 2007; Simunovic et al. 2016; Simunovic et al. 2013). Indeed, disrupting the ability of BAR domain proteins to form such two-dimensional lattices through mutagenesis impairs their ability to sculpt liposomes in vitro and membranes in cells (Frost et al. 2008; Pykalainen et al. 2011; Shimada et al. 2007). Furthermore, while the F-BAR domain of CIP4 and FBP17 forms helical coats on membrane tubules via lateral and tip-to-tip interactions (Frost et al. 2008), the N-BAR domain of Endophilin forms a lattice that is held together primarily through interactions between the extended N-terminal amphipathic helices of neighboring Endophilin molecules (Mim et al. 2012). As a result, the Endophilin lattice exposes larger areas of membrane surface than CIP4 and FBP17, which form more densely packed lattices.

Another factor influencing membrane binding by BAR domain proteins is coincidence detection, whereby other domains participate along with the BAR domain in membrane binding (Moravcevic et al. 2012). Examples include cooperative membrane binding by the PX-BAR module of sorting nexins (Lo et al. 2017; Pylypenko et al. 2007; Yarar et al. 2008), the BAR-PH module of ASAP/ACAP-family members (Peter et al. 2004), and the PDZ-BAR module of PICK1 (Jin et al. 2006; Pan et al. 2007) (more below about the role of auxiliary domains).

Multi-domain structure of BAR domain proteins, autoinhibition, and Rho GTPase regulation

The BAR domain is rarely found in isolation, as most members of this superfamily contain one or more auxiliary domains (Fig. 1). Some of the existing crystal structures show either auxiliary domains or GTPases interacting tightly with BAR domains (Fig. 5) (Boczkowska et al. 2015). The auxiliary domain most commonly found among BAR domain proteins is the SH3 domain, present in ~ 50% of all BAR domain proteins, either as a single or multiple copies. The presence of the SH3 domain is a strong indicator of interactions with actin cytoskeleton assembly factors and/or the GTPase dynamin. The actin assembly factors most commonly recruited by BAR domain proteins include nucleation promoting factors (NPFs) of the Arp2/3 complex (Suetsugu and Gautreau 2012) and actin nucleation and elongation factors such as formins (Fujiwara et al. 2000; Garabedian et al. 2018; Goh et al. 2012b; Graziano et al. 2014; Willet et al. 2015; Yan et al. 2013) and Ena/VASP-family proteins (Cestra et al. 2005; Chou et al. 2014; Disanza et al. 2013; Krugmann et al. 2001; Lim et al. 2008; Oikawa et al. 2013; Salazar et al. 2003; Vehlow et al. 2013), all of which contain Pro-rich sequences that mediate these interactions (Dominguez 2016). NPFs, in particular, activate the nucleation activity of the Arp2/3 complex, and in this way, they control the time and location for branched actin network assembly in cells (Pollard 2007).

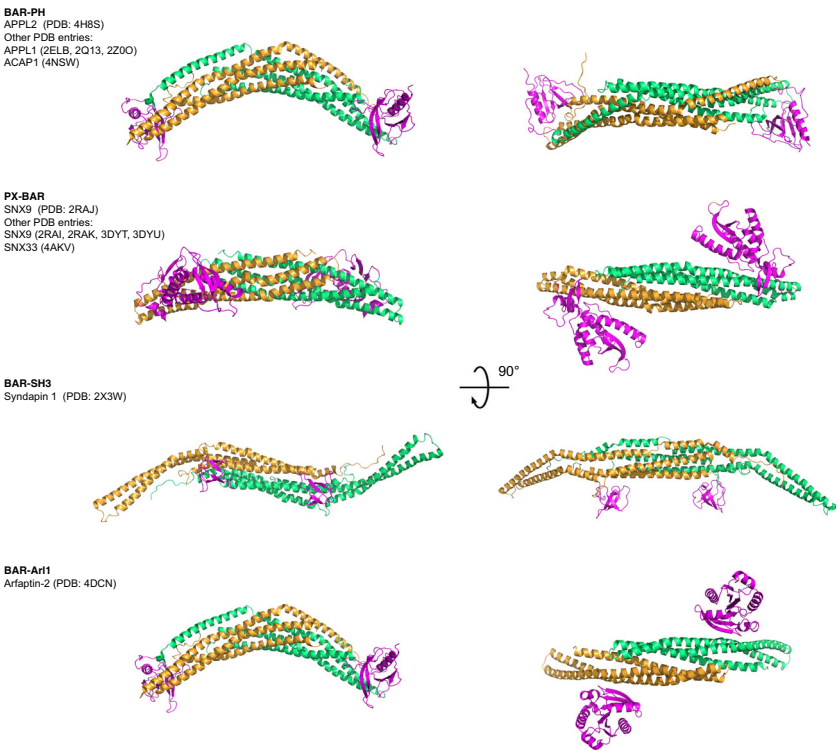

Fig. 5 Structures of BAR domain proteins showing tightly interacting auxiliary domains. The PDB codes of the structures are shown, as well as those of related structures. BAR domain dimers are colored orange and green, and the auxiliary domains (or GTPase) are colored magenta. For each structure, two perpendicular views are shown. Only one SH3 domain was resolved in the structure of Syndapin 1; the second SH3 domain was generated by symmetry

Another way in which BAR domain proteins control actin cytoskeleton remodeling is through their ability to regulate Rho-family GTPases (Aspenstrom 2014; de Kreuk and Hordijk 2012). Rho GTPases are master regulators of actin assembly dynamics (Hall 2012; Ridley 2015), acting as molecular on/off switches as they cycle between active GTP-bound and inactive GDP-bound states (Ridley 2012). This cycle is regulated by two types of proteins: *G*uanine nucleotide *E*xchange *F*actors (GEFs), which catalyze the exchange of GDP for GTP to activate Rho GTPases, and *G*TPase *A*ctivating *P*roteins (GAPs), which stimulate the catalytic activity to inactivate Rho GTPases (Bos et al. 2007). Additionally, some Rho GTPases are regulated by *G*uanine nucleotide *D*issociation *I*nhibitors (GDIs), which sequester Rho GTPases in their inactive conformation (Garcia-Mata et al. 2011). Approximately 35% of all BAR domain proteins either contain ArfGAP, RhoGAP, or RhoGEF domains and regulate the activities of various GTPases or are themselves regulated by Rho-family GTPases (de Kreuk and Hordijk 2012) (Fig. 1). Direct regulation by Rho GTPases has been reported for all members of the I-BAR subfamily, including IRSp53 (Abou-Kheir et al. 2008; Disanza et al. 2013; Kast et al. 2014; Krugmann et al. 2001; Lim et al. 2008; Miki et al. 2000), MIM (Bompard et al. 2005; Drummond et al. 2018), ABBA (Saarikangas et al. 2008; Zeng et al. 2013; Zheng et al. 2010), IRTKS (Sudhaharan et al. 2016), and Pinkbar (Sudhaharan et al. 2016), as well as the BAR domain protein Arfaptin (D'Souza-Schorey et al. 1997; Van Aelst et al. 1996), and the F-BAR family-members Toca1 (Bu et al. 2010; Ho et al. 2004; Watson et al. 2016), CIP4 (Aspenstrom 1997; Pichot et al. 2010), and Syndapin 2 (PACSIN2) (de Kreuk et al. 2011). Although not specifically reviewed here, phosphorylation-dependent signaling also abounds among BAR domain proteins, several of which are either directly phosphorylated or contain themselves tyrosine kinase domains that regulate downstream effectors, including cytoskeletal proteins (Craig 2012).

One more consequence of the multi-domain organization of BAR domain proteins is autoinhibition, as many auxiliary domains moonlight as inhibitory domains. Indeed, examples abound among cytoskeletal proteins of domains implicated in autoinhibition that expose a different functional surface upon activation, including the DAD (*D*iaphanous *A*utoregulatory *D*omain) domain of certain formins (Gould et al. 2011) and the C-region of WASP-family NPFs (Panchal et al. 2003), which both play dual roles in autoinhibition and actin nucleation. Among BAR domain proteins, autoinhibition can affect membrane binding, interactions with downstream effectors, regulation of Rho GTPases, or a combination of these functions. Two well-documented examples, demonstrated at the cellular, biochemical, and structural levels include the inhibition of IRSp53 and Syndapin 1. In IRSp53, autoinhibition involves an intramolecular interaction between the CRIB-PR and SH3 domains (Kast et al. 2014; Krugmann et al. 2001), and is additionally reinforced by binding of 14-3-3 to phosphorylation sites located mainly in the region between the CRIB-PR and SH3 domains (Cohen et al. 2011; Robens et al. 2010). Binding of Cdc42 to the CRIB-PR and/or cytoskeletal effectors to the

Table 1 Autoinhibition of BAR domain proteins

Protein	Autoinhibition and references
PICK1	Adopts an autoinhibited conformation, characterized by its uniform cytoplasmic localization, in which the membrane-binding surface of the BAR domain is masked (Lu and Ziff 2005; Madasu et al. 2015; Madsen et al. 2008; Perez et al. 2001). Deletion of the PDZ domain or binding of the PDZ domain to a ligand at the membrane exposes the membrane-binding capacity of the BAR domain, resulting in PICK1 relocalization to vesicle-like clusters
Amphiphysin	Binding to membranes depends on dynamin binding to the SH3 domain, which relieves SH3-BAR autoinhibitory interactions (Meinecke et al. 2013)
BIN1	Pro-rich peptides that bind to the SH3 domain relive autoinhibitory BAR-SH3 domain interactions (Wu and Baumgart 2014)
Endophilin	Binding to membranes depends on dynamin binding to the SH3 domain, which relieves SH3-BAR autoinhibitory interactions (Meinecke et al. 2013)
RICH1	An intramolecular interaction between the BAR and RhoGAP domains inhibits the GAP activity (Beck et al. 2013)
GRAFs	An intramolecular interaction between the BAR and RhoGAP domains inhibits downregulation of Rho GTPase activity via the GAP domain (Eberth et al. 2009; Fauchereau et al. 2003)
ASAP1	An interaction between the BAR domain and the PH and ArfGAP domains inhibits the ArfGAP activity (Jian et al. 2009)
FCHSD2	In cells, the SH3 domains control the protrusion formation activity of the BAR domain (Almeida-Souza et al. 2018), as also observed with the *Drosophila* homolog Nwk in which the autoinhibitory activity of the SH3 domain is modulated by its interaction with N-WASP (Stanishneva-Konovalova et al. 2016)
Syndapins	Binding to membranes depends on dynamin binding to the SH3 domain, which relieves SH3-BAR autoinhibitory interactions (Goh et al. 2012a; Rao et al. 2010; Senju et al. 2011; Wang et al. 2009)
SRGAP2	Autoinhibited by intramolecular interaction between the F-BAR and SH3 domains, released upon effector binding to the SH3 domain (Guerrier et al. 2009)
ARHGAP45	An intramolecular interaction between the BAR and RhoGAP domains inhibits the GAP activity (de Kreuk et al. 2013)
IRSp53	Inhibited through an intramolecular interaction between the CRIB-PR and SH3 domains (Kast et al. 2014; Krugmann et al. 2001) that is reinforced by binding of 14-3-3 to phosphorylation sites within the region between the CRIB-PR and SH3 domains (Cohen et al. 2011; Robens et al. 2010)

SH3 domains synergistically activates IRSp53 (Kast et al. 2014). It is still unknown, however, how 14-3-3-dependent inhibition is relieved, although it is likely to involve dephosphorylation of IRSp53. In Syndapin 1, the SH3 domain internally inhibits the membrane deformation activity of the F-BAR domain, and association of the SH3 domain with Pro-rich sequences in downstream effectors such as dynamin releases this inhibitory interaction and exposes the membrane-binding activity of the F-BAR domain (Goh et al. 2012a; Rao et al. 2010; Wang et al. 2009). Table 1 summarizes documented examples of autoinhibition among BAR domain proteins.

BAR domain proteins coordinate actin cytoskeleton and membrane remodeling

The membrane tubulation activity of BAR domain proteins was first established for Amphiphysin (Takei et al. 1999) and Endophilin (Farsad et al. 2001), whereas their ability to regulate actin dynamics was reported even earlier for Rvs167, the yeast homolog of Amphiphysin, which was found to play crucial roles in actin assembly (Sivadon et al. 1995) and endocytosis (Munn et al. 1995). However, it was only around 2005 that it started to emerge that BAR domain proteins acted as multifunctional hubs, coordinating these two types of activities along with signaling cues to regulate numerous cellular processes, and in particular membrane trafficking (Cestra et al. 2005; Dawson et al. 2006; Ferguson et al. 2009; Itoh and De Camilli 2006; Itoh et al. 2005; Kessels and Qualmann 2004; McMahon and Gallop 2005; Shimada et al. 2007; Tsujita et al. 2006) and the formation of cell protrusions (Mattila et al. 2007; Millard et al. 2005; Suetsugu et al. 2006). Since these initial studies, most BAR domain proteins have now been linked to actin assembly pathways, and it is becoming increasingly clear that this large family of proteins provides probably the most diverse and widespread link between membranes and the actin cytoskeleton. As mentioned above, such linkages often involve regulation of actin assembly through effects on Rho-family GTPases (de Kreuk and Hordijk 2012) or direct recruitment of NPFs of the Arp2/3 complex (Suetsugu and Gautreau

Table 2 Coordination of membrane remodeling and actin assembly by BAR domain proteins

Protein	Function and references
PICK1	Studies disagree as to whether PICK1 inhibits Arp2/3 complex; one study reported that PICK1 inhibits actin filament nucleation by the Arp2/3 complex through interactions of its BAR domain with filamentous actin and its acidic C-terminal tail with Arp2/3 complex, which allegedly reduces membrane tension for endocytosis (Rocca et al. 2008). However, another study found that PICK1 does not bind nor inhibits Arp2/3 complex, but does associate with fast-moving vesicles, which move in a manner consistent with myosin-driven motility (Madasu et al. 2015)
Amphiphysin	Implicated in actin remodeling during endocytosis, phagocytosis, and T-tubule formation via its recruitment of N-WASP and the Arp2/3 complex assembly machinery (Butler et al. 1997; Yamada et al. 2007; Yamada et al. 2009)
BINs	Implicated in T-tubule biogenesis in muscle cells in an N-WASP/Arp2/3 complex-dependent manner (Hong et al. 2014; Lee et al. 2002) BIN1/N-WASP-dependent actin assembly is required for nuclear positioning and triad organization in skeletal muscle (Falcone et al. 2014) BIN1 links the nuclear envelope to the actin and microtubule cytoskeletons to position and shape the nucleus (D'Alessandro et al., Dev Cell. 2015) BIN2 is highly expressed in leukocytes, where it controls podosome formation, motility, and phagocytosis. It associates with actin-rich structures on the plasma membrane and via its Pro-rich C-terminal region recruits SH3-containing partners such as Endophilin-A2 and αPIX (Sanchez-Barrena et al. 2012) BIN3 colocalizes with F-actin in lamellipodia, where it forms a complex with Rac1 and Cdc42 and promotes the migration of differentiated muscle cells during early myogenesis (Simionescu-Bankston et al. 2013)
Endophilins	Participate along with dynamin and the actin cytoskeleton in plasma membrane invagination during endocytosis (Itoh et al. 2005) In cells lacking dynamin, actin-nucleating proteins, actin, and several BAR domain proteins (Endophilin, BINs, SNX9, and SNX18) accumulate at the base of arrested endocytic clathrin-coated pits, where they support the growth of dynamic long tubular necks (Ferguson et al. 2009) Directly interact with both lamellipodin and MENA to mediate EGFR endocytosis in an actin-dependent manner (Vehlow et al. 2013) Act together with dynamin and actin to drive a fast form of clathrin-independent endocytosis at PIP2-rich sites (Boucrot et al. 2015; Renard et al. 2015) Promotes actin polymerization in dendritic spines and its loss causes impaired AMPA receptor-mediated synaptic transmission and long-term potentiation (Yang et al. 2018)
RICHs	RICH1 (ARHGAP17) regulates Rho GTPases through its GAP domain to mediate the formation of stress fibers and focal adhesions in platelets (Beck et al. 2013) RICH2's (ARHGAP44) recruitment to nanoscale membrane deformations limits filopodia initiation via Rac inhibition mediated by its GAP domain, which in turn reduces actin polymerization required for filopodia formation (Galic et al. 2014)
GRAFs	Owing to their Rho-GAP-dependent actin remodeling and BAR domain-dependent membrane sculpting activities, GRAF 1 and 2 promote myoblast fusion in muscles (Doherty et al. 2011) GRAF1's RhoGAP domain exhibits strong GTPase-stimulating activity towards RhoA, Cdc42, and Rac1, which regulates cell adhesion and spreading through effects on the actin cytoskeleton, including the formation of stress fibers, focal adhesions, filopodia, and lamellipodia (Elvers et al. 2012) GRAF3's RhoA GAP activity is regulated through Src-mediated tyrosine phosphorylation to control focal adhesion dynamics and promote cell motility (Luo et al. 2017)
ASAP1	Controls invadopodia formation, and this activity requires the presence of the BAR and SH3 domains and Src tyrosine kinase-mediated phosphorylation (Bharti et al. 2007)
Tuba	The four N-terminal SH3 domains bind dynamin, which is critical for the fission of endocytic vesicles. The RhoGEF domain activates Cdc42. The C-terminal SH3 domain binds N-WASP and Ena/VASP, which promotes actin polymerization. In this way, Tuba links membrane deformation, dynamin activity and actin dynamics during endocytosis (Cestra et al. 2005; Salazar et al. 2003)
SNX33	Plays a role in maintaining cell shape and cell cycle progression through its interaction with WASP (Zhang et al. 2009)
FES	Through the coordinated actions of the F-BAR, SH2 and tyrosine kinase domains, FES couples signaling via the high-affinity immunoglobulin G receptor (FcεRI) and actin reorganization in mast cells to support endocytosis and chemotaxis (McPherson et al. 2009)
FCHSDs	Expressed in hair cell stereocilia and cuticular plate. FCHSD2 (but not FCHSD1) interacts with WASP and N-WASP via its SH3 domains and stimulates actin assembly in vitro, whereas FCHSD1 colocalizes and interacts with another BAR domain protein, SNX9, and enhances its WASP-Arp2/3 complex-dependent actin polymerization activity (Cao et al. 2013) FCHSD2 recruits N-WASP to PIP_2-rich membrane domains at the base of clathrin-coated pits to promote Arp2/3 complex-dependent actin polymerization for pit maturation (Almeida-Souza et al. 2018)
Syndapins (PACSINs)	Provide a link between the actin cytoskeleton and membrane remodeling by interacting with membranes, dynamin, and N-WASP. Function in endocytic and vesicle trafficking events important for neuronal morphogenesis and cell migration (Andersson et al. 2008; Dharmalingam et al. 2009; Modregger et al. 2000; Qualmann and Kelly 2000; Qualmann et al. 1999; Quan and Robinson 2013) Form a complex with polycystin-1 at the membrane and recruit N-WASP and the Arp2/3 complex to initiate actin assembly and modulate directional epithelial cell migration, which contributes to the establishment and maintenance of tubular structures (Yao et al. 2014) Interact with and act synergistically with the actin nucleator cordon-bleu (Cobl) in the formation of actin-rich stereocilia, playing roles in dendritic arborization (Schwintzer et al. 2011) and sensory hair cell formation (Schuler et al. 2013)
Toca-1	Participates along with dynamin and the actin cytoskeleton in plasma membrane invagination during endocytosis (Itoh et al. 2005) Mediates Cdc42-dependent actin nucleation by activating N-WASP (Aspenstrom 1997; Ho et al. 2004), and this activity is strongly enhanced in the presence of liposomes of a specific diameter (Gallop et al. 2013; Takano et al. 2008). Integrates membrane trafficking and actin dynamics through WASP and SCAR/WAVE (Fricke et al. 2009) Induces the formation of filopodia and endocytic vesicles in neuroblastoma cells (Bu et al. 2009) and is implicated in membrane tubulation and vesicle formation and motility in CHO and HeLa cells (Bu et al. 2010) Mediates the recruitment and activation of N-WASP and the Arp2/3 complex for actin comet tail formation and motility of *Shigella flexneri* (Leung et al. 2008)

Table 2 (continued)

Protein	Function and references
	Implicated in trafficking events downstream of Cdc42 that require actin polymerization by the Arp2/3 complex in mammalian cells and *C. elegans* (Bai and Grant 2015)
	Forms a complex with ZO-1 and recruits N-WASP at tight junctions to induce actin assembly dynamics for proper maintenance of cell-cell contacts (Van Itallie et al. 2015)
FBP17 (Toca-2)	Participates along with dynamin and the actin cytoskeleton in plasma membrane invagination during endocytosis (Itoh et al. 2005; Kamioka et al. 2004; Shimada et al. 2007; Tsujita et al. 2006) and podosome and phagocytic cup formation in macrophages (Tsuboi et al. 2009), and this activity is antagonized by another F-BAR protein, PSTPIP2 (Tsujita et al. 2013)
CIP4 (Toca-3)	Coordinates actin assembly downstream of Cdc42 through interactions with membranes, dynamin and WASP-family proteins (Aspenstrom 1997) for plasma membrane invagination during endocytosis (Itoh et al. 2005; Tsujita et al. 2006)
	Implicated alongside FBP17 in phagocytic cup formation (Dombrosky-Ferlan et al. 2003)
	Promotes GLUT4 endocytosis through bidirectional interactions with N-WASp and Dynamin-2 (Hartig et al. 2009)
	Regulates platelet-derived growth factor (PDGF) beta-receptor internalization downstream of Cdc42, impacting actin assembly and cell migration (Toguchi et al. 2010)
	Is essential for integrin-dependent T cell trafficking (Koduru et al. 2010)
	Its loss impairs membrane-cytoskeleton remodeling and reduces platelet production (Chen et al. 2013)
SRGAPs	SRGAP2 integrates cell edge curvature and Slit-Robo-mediated repulsive cues to fine-tune Rac1 activation dynamics and elicit fibroblast contact inhibition of locomotion (CIL) (Fritz et al. 2015)
	SRGAP3 regulates cytoskeletal reorganization through inhibition of the Rho GTPase Rac1 and interaction with actin remodeling proteins, playing a role in the development of dendritic spines. Disruption of SRGAP3 leads to intellectual disability in humans (Bacon et al. 2013)
ARHGAP45 (HMHA1)	Regulates cytoskeletal remodeling and cell spreading through its RhoGAP activity (de Kreuk et al. 2013)
IRSp53	Interacts with Rac and induces membrane deformation in a Rac-dependent manner (Suetsugu et al. 2006)
	The synergic bundling activity of the IRSp53-Eps8 complex, regulated by Cdc42, contributes to the generation of filopodial protrusions (Disanza et al. 2006)
	Deforms PIP_2-rich membranes through an inverse BAR domain-like mechanism (Mattila et al. 2007), playing a role in the formation of cell protrusions such as filopodia by coordinating membrane and actin cytoskeleton dynamics (Kast et al. 2014; Lim et al. 2008; Yang et al. 2009)
	Enterohemorrhagic *E. coli* (EHEC) recruits IRSp53 at the membrane through an interaction with its translocated effector protein Tir that inserts into the plasma membrane. IRSp53 in turn recruits the secreted bacterial virulence factor EspFu, which then recruits and activates N-WASP, leading to Arp2/3 complex-dependent actin polymerization for pedestal formation (Vingadassalom et al. 2009; Weiss et al. 2009)
	Associates in a phosphorylation dependent manner with 14-3-3, which inhibits binding of its SH3 domain to cytoskeletal proteins such as WAVE2 and Eps8, and prevents binding of Cdc42, resulting in shorter filopodia lifetimes (Cohen et al. 2011; Robens et al. 2010)
	Cdc42 switches IRSp53 from inhibition of actin growth to elongation by clustering VASP (Disanza et al. 2013)
	Recruits the actin filament elongation factor VASP through its SH3 domain, and this interaction is essential for podosome formation (Oikawa et al. 2013)
	While bound to the plasma membrane at the tip of filopodia through interaction with Cdc42 and the membrane via the I-BAR domain, the SH3 domain sequentially switches binding partners between dynamin-1, Mena and Eps8 for filopodia initiation, assembly, and disassembly, respectively (Chou et al. 2014)
	Recruited and activated by Cdc42 at sites of clathrin and dynamin-independent endocytosis, which in turn recruits Arp2/3 complex-dependent actin polymerization for endocytosis (Sathe et al. 2018)
MIM	Deforms PIP_2-rich membranes through an inverse BAR domain-like mechanism, playing a role in the formation of cell protrusions such as filopodia and dendritic spines (Mattila et al. 2007). Some isoforms contain a C-terminal WH2 domain, which recruits monomeric actin (Lee et al. 2007)
	Promotes Arp2/3 complex-dependent actin filament assembly at intercellular junctions and is required for integrity of kidney epithelia intercellular junctions (Saarikangas et al. 2011)
	Its knockout in mouse embryonic fibroblasts impairs cell polarity and the motility response to growth factors via effects on the actin cytoskeleton (Yu et al. 2011)
	Through its I-BAR domain, MIM accumulates at transendothelial cell macroaperture (TEM) tunnels induced by *Bacillus anthracis* edema toxin and triggers Arp2/3 complex-dependent actin polymerization, which reseals the TEM (Maddugoda et al. 2011)
	Accumulates at spine initiation sites in a PIP_2-dependent manner to begin the outward deformation of the plasma membrane. This is followed by recruitment of the Arp2/3 complex assembly machinery required for spine elongation and proper synaptogenesis (Saarikangas et al. 2015)

2012). In Table 2, we compile existing evidence linking BAR domain proteins to cytoskeleton remodeling events, focusing specifically on mammalian BAR domain proteins.

Several studies have also shown that some BAR domains (taken in isolation) can bind actin filaments directly and influence actin polymerization in vitro (Drager et al. 2017; Kostan et al. 2014; Millard et al. 2005; Rocca et al. 2008), which is mechanistically understandable given the overall positive charge of the membrane binding-surface of the BAR domain and the presence of a negatively charged helical rim along the long-pitch helix of the actin filament. However, the functional significance of such interactions is unclear, since they are intrinsically incompatible with membrane binding, which uses the same positively charged surface on the BAR domain and

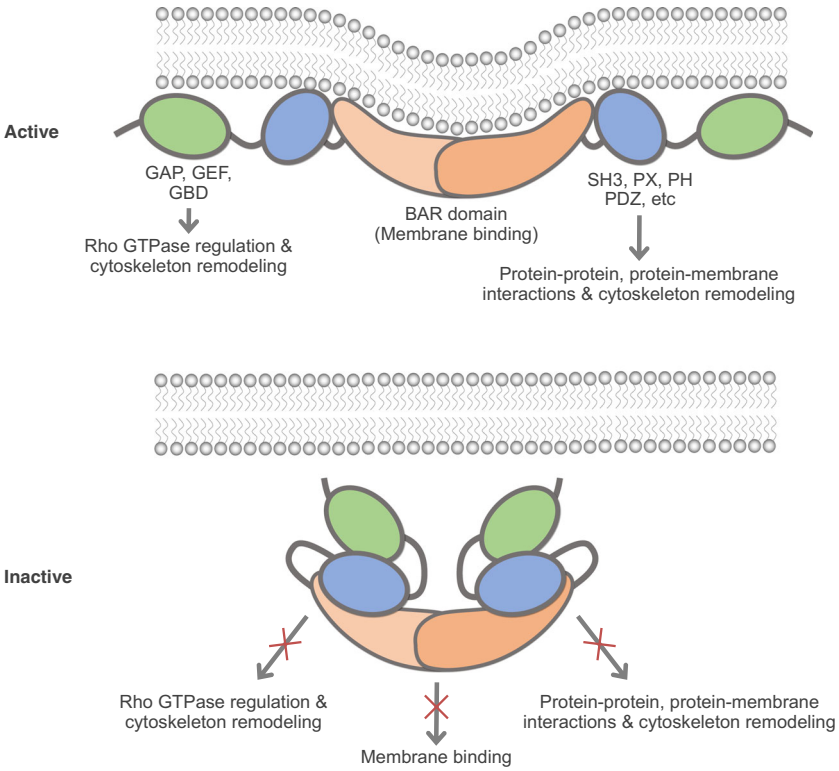

Fig. 6 Diagram showing a prototypical BAR domain protein in the active and inactive states. In most BAR domain proteins characterized thus far, interaction sites with membranes, downstream effectors and GTPases are exposed as a result of a conformational change upon activation

is the primary function of this domain. Furthermore, we must consider that actin filaments in cells are heavily decorated with filamentous actin-binding proteins. Most notably, a recent study found that up to 80% of actin filaments in cells are decorated with one of over 40 existing tropomyosin isoforms (Meiring et al. 2018), whose binding site along the long-pitch helix of the actin filament (Dominguez 2011; Li et al. 2011) overlaps with the proposed binding surface of the BAR domain (Kostan et al. 2014). It is nevertheless conceivable that under regulation BAR domains could switch between binding to actin filaments and membranes, which remains to be further explored.

Interactions among BAR domain proteins—a combinatorial toolkit for membrane remodeling

BAR-BAR heterodimerization (or interaction) could be another factor expanding the range of activities mediated by BAR domain proteins. Indeed, numerous BAR domain proteins have been reported to associate with one another, including mammalian BIN1 and BIN2 (Ge and Prendergast 2000); BIN1 and Amphiphysin (Ramjaun et al. 1999; Slepnev et al. 1998; Wigge et al. 1997) and their yeast and *C. albicans* orthologs (Friesen et al. 2006; Gkourtsa et al. 2015; Lombardi and Riezman 2001; Youn et al. 2010); the F-BAR proteins SRGAP1, SRGAP2, and SRGAP3 (Coutinho-Budd et al. 2012); sorting nexins SNX1, SNX2, SNX5, and SNX6 (Haft et al. 1998; Parks et al. 2001; Wassmer et al. 2007) and their yeast orthologs (Seaman and Williams 2002); BIN1 and SNX4 (Leprince et al. 2003); FCHSD1 and FCHSD2 (Cao et al. 2013); and PICK1 and ICA69/ICA1L (Cao et al. 2007; He et al. 2015; Holst et al. 2013). However, it is unclear whether these proteins associate through actual heterodimerization or via side-by-side interaction of intact homodimers, since the dissociation of some BAR domain dimers appears unlikely given the extremely large hydrophobic interface buried by dimerization. Independent of this consideration, this is a topic that deserves further investigation, since in principle, the combinatorial association of BAR domain proteins could considerably expand the spectrum of membrane curvature and partner recruitment activities of this family of proteins. Finally, non-molecular factors, including external physical forces applied on the membrane (tension and friction) have been also suggested to impact the ability of BAR domain proteins to remodel membranes (Nishimura et al. 2018).

In summary, a prototypical BAR domain protein is one that has a membrane-binding and antiparallel dimerization BAR domain of variable size and curvature (Fig. 6). Almost invariably, these proteins feature auxiliary domains, which are typically implicated in the recruitment of actin cytoskeleton assembly factors or regulation of Rho-family GTPases, which in turn also regulates actin assembly. These auxiliary domains often participate along with the BAR domain in membrane binding. In the resting, inactive state, many BAR domain proteins exist in compact autoinhibited conformations and upon activation, triggered by binding to effectors and/or membranes, undergo large conformational changes that expose

the membrane-binding surface of the BAR domain, as well as protein-protein or protein-membrane interaction sites in the auxiliary domains. The spectrum of actin assembly activities associated with BAR domain proteins is constantly increasing, and thus this will likely continue to be a very active area of research. Also underexplored remain the structural mechanisms of membrane tubulation, as well as the potential connections between BAR domain proteins and molecular motors of the myosin, dynein, and kinesin families that could together drive efficient membrane deformation events (McIntosh et al. 2018). Finally, through combinatorial BAR-BAR association, the potential for BAR domain protein-dependent activities increases exponentially, opening exciting new prospects for future investigation.

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Compliance with ethical standards

Conflict of interest Peter J. Carman declares that he has no conflict of interest. Roberto Dominguez declares that he has no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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