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Review Article

BAR proteins in cancer and blood disorders

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Abstract: Remodeling of the membrane and cytoskeleton is involved in a wide range of normal and pathologic cellular function. These are complex, highly-coordinated biochemical and biophysical processes involving dozens of proteins. Serving as a scaffold for a variety of proteins and possessing a domain that interacts with plasma membranes, the BAR family of proteins contribute to a range of cellular functions characterized by membrane and cytoskeletal remodeling. There are several subgroups of BAR proteins: BAR, N-BAR, I-BAR, and F-BAR. They differ in their ability to induce angles of membrane curvature and in their recruitment of effector proteins. Evidence is accumulating that BAR proteins contribute to cancer cell invasion, T cell trafficking, phagocytosis, and platelet production. In this review, we discuss the physiological function of BAR proteins and discuss how they contribute to blood and cancer disorders.

Keywords: BAR proteins, GTPases, WASP, blood, cancer

Introduction

Eukaryotic cells must change their shape to perform critical biological functions such as embryonic development, immune surveillance, and motility [1]. Structural changes also underlie disease processes, such as wound healing or cancer cell invasion. Changes in cell shape and motility depend heavily upon a tight coupling between the actin cytoskeleton and plasma membrane of the cell. The actin cytoskeleton provides flexibility to cells enabling them to achieve various shapes to perform various cellular behaviors. During cell shape change, remodeling of actin cytoskeleton and recruitment of several actin associated proteins provide the mechanical force to propel the cell. In addition to cell shape change and motility, the actin cytoskeleton is also required for protrusion formation and invagination of plasma membrane, resulting in vesicle formation and its content release or fusion with the endolysosomal membrane trafficking. Endocytosis is required for trafficking proteins, recycling of plasma membrane, as well as for uptake and down regulation of cell-surface receptors. Endocytic processes can also be usurped by pathogens, allowing their entry into cells [2-7].

Recent reports have established that Bin-Amphiphysin-Rvs (BAR) domain proteins play a major role in endocytosis [8]. The BAR superfamily of proteins consists of I-BAR, N-BAR, and F-BAR proteins (**Figure 1A**). These proteins bend the membrane during endocytosis and couple the membrane with actin cytoskeleton to mold the cytoarchitecture [9]. BAR proteins function as scaffolding proteins by binding to the membrane and recruiting cytoskeletal regulatory proteins such as the Rho GTPase Cdc42, the actin nucleator (N)-WASP, the large GTPase involved in membrane scission dynamin, and Src family kinases. Knock-down or knock-out studies established the roles of BAR proteins in clathrin-dependent and -independent endocytosis [10, 11]. Members of this protein superfamily play a crucial role in T-tubule formation in muscle cells, cell motility, and neuromorphogenesis [12-16]. BAR proteins are also involved in epithelial architecture, regulating apical-polarity proteins in epithelial cells and maintaining tight junctions [17] or planar membrane structures [18]. Mutations in the gene encoding the BAR protein have been implicated in several diseases such as bladder carcinoma, auto-inflammatory diseases, and Huntington's disease [19, 20]. In this review, we discuss the various classes of BAR

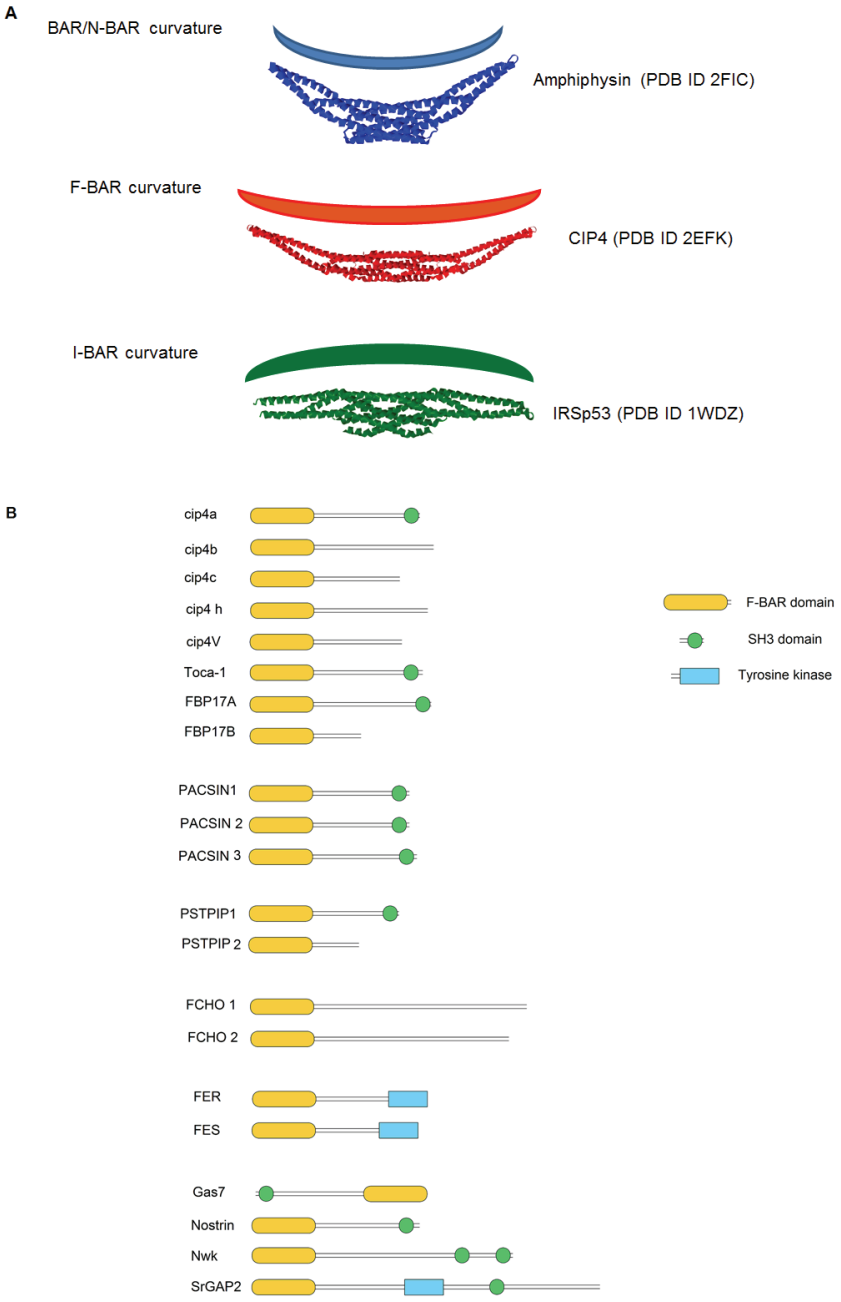

Figure 1. Comparison of BAR proteins. A) Curvatures of different types of BAR domains. F-BAR domain-containing proteins have a shallower curvature than BAR/N-BAR domains. Shown are molecular structures from the Protein Data Base: N-BAR protein Amphiphysin [95] (PDB ID: 2FIC), F-BAR protein CIP4 [46] (PDB ID: 2EFK), and I-BAR protein IRSp53 (PDB ID: 1WDZ, by Murayama K, Suetsugu S, Seto A, Shirouzu M, Takenawa T, Yokoyama S. Crystal structure of RCB domain of IRSp53, not published yet). B) Structure-function domains of F-BAR proteins. Several F-BAR proteins have an SH3 domain; Nwk has two SH3 domains; FER, FES and srGAP2 have a tyrosine kinase domain. Adapted and Modified form Chitu V et al, 2007 [96].

domains and how these proteins play a critical role in regulation of endocytosis as well as cancer progression. Finally, we describe the importance of BAR proteins in blood disorders.

Structure-function of bar proteins: N-BAR, F-BAR, and I-BAR

The BAR domain was originally identified as an evolutionary conserved region shared by the yeast proteins Rvs161, Rvs167 and the metazoan amphiphysins (the splice variants of which are also called Bin1) [21, 22]. BAR superfamily of proteins has been classified in several subfamilies such as BAR, N-BAR (BAR proteins that contain N-terminal amphipathic helix), I-BAR/ IMD (Inverse BAR/ IRSp53 -MIM homology domain), and EFC/FCH-BAR/PHC (Fes/CIP4 homology BAR) or pombe Cdc15 homology (PCH) domain (**Figure 1A**). These proteins have emerged as a central regulator of membrane curvature in all eukaryotes [19, 23]. BAR proteins link the actin cytoskeleton to the plasma membrane and helps to form tubules during endocytosis [24-26].

The BAR domain of amphysin was the first to be identified, crystallized, and found to be deform the plasma membrane [23]. These findings fur-

ther confirmed the role of BAR proteins in membrane trafficking and endocytosis. The crystal structures of fifteen BAR proteins have now been now solved, revealing that BAR proteins tend to form homodimers with the help of three anti-parallel coiled-coil motifs and may stabilize or deform the membrane curvature [23, 27]. With the insertion of amphipathic motifs in the membrane, BAR proteins induce membrane curvature that corresponds to the membrane binding properties of these proteins [28]. The three dimensional arrangement of these amphipathic motifs differ slightly in various BAR proteins which is the basis of their classification. BAR proteins have highly specific membrane curvature preferences. The classic BAR domains use their positively charged amino acid at the concave surface to interact with the negatively charged inner surface of the cell membrane mostly through the interaction with phospholipids. Three anti-parallel alpha helices of each monomeric BAR domain forms crescent-shaped/or banana shaped homodimeric BAR domains with six alpha helical bundles which aid in sensing and creating curvature to the cell membrane during endocytosis. *In vitro* studies have confirmed that purified BAR domains and its mutants can penetrate into the lipid membrane and tubulates liposome [28]. However, the regulation of membrane deformation induced by BAR proteins as well as its molecular mechanism is still obscure.

BAR domain proteins such as amphiphysin, endophilin, and Tuba contain an Src homology 3 (SH3) domain which interacts with proteins that contain polyproline-rich motif such as that found in (N)-WASP and dynamin (**Figure 1B**). These findings suggest that membrane fission capability of BAR domain proteins are tightly coupled with the tight regulation of actin polymerization and dynamin GTPase activity [19]. In addition to the BAR and SH3 domains, BAR proteins sometimes also contain a pleckstrin homology (PH) [29, 30] or a PX domain [31]. The PH domain binds phosphatidylinositol lipids, most notably PtdIns-(4,5)-P_2 or PtdIns-(3,4,5)-P_3 [32, 33]. The PX domain also interacts with phosphoinositides. Thus, the PH or PX domains strengthen the binding of BAR proteins at specific locations in the cell membrane to induce specific membrane curvature.

N-BAR proteins have the same overall domain structure as BAR proteins and contain an additional N-terminal amphipathic alpha helix that penetrates into the lipid bilayer [34, 35]. With the N-BAR domain, N-terminal amphipathic alpha helices penetrate the hydrophobic phase of the lipid bilayer and thus displace the phospholipid of the lipid bilayer and create a positive curvature in the cell membrane [34, 35]. The crystal structure of the N-BAR endophilin reveals an additional conserved amphipathic alpha helix at the center of the BAR domain that helps with the insertion of the BAR domain into the lipid bilayer. Thus, the N-BAR domain promotes the stability of membrane curvature [34-37]. Extra amphipathic alpha helices may contribute to the high degree of tubulation as well as increase the amount of time it takes endophilin to reach the membrane during vesicle formation. When compared with amphiphysin, this is vastly different suggesting a disparity in the role of these proteins at the regulation of vesicle formation. This could explain the need for different BAR proteins during the various stages of endocytic vesicle formation. Through their C-terminal SH3 domain, the N-BAR proteins can interact with dynamin or synaptojanin (**Figure 1B**) [38].

I-BAR proteins (I is for inverse) bind to the membrane but are associated with a convex, not concave, curvature (**Figure 1A**). Interacting with WAVE, they contribute to membrane protrusion and lamellipodida formation [39]. IRS-p53 is another I-BAR protein that regulates membrane ruffling through WAVE and Rac [40-42]. Missing-In-Metastasis binds actin [43] and interacts with cortactin and N-WASP to regulate actin polymerization [44]. The recently described I-BAR protein Pinkbar interacts with phospholipids to induce a planar structure [18]. Since Pinkbar is found in Rab13-associated vesicles in intestinal or renal epithelial cells, it may function to tight junction assembly.

F-BAR proteins were originally recognized as FER-CIP4 homology (FCH) domain at the N-terminal region and were known as the coupling proteins between endocytic machinery and actin cytoskeleton (**Figure 1B**) [45]. Sequence analysis and crystallographic structure analysis of several F-BAR proteins established sequence similarity between FCH and BAR domain [24, 46]. The F-BAR proteins can tubulate membranes *in vivo* as well as *in vitro* [24, 47, 48]. As compared with classical BAR or N-BAR proteins, F-BAR proteins generate greater concave surface with a more shallow curvature for mem-

brane tubulation [28, 46]. Thus, F-BAR proteins can exert greater force for a wider, thicker tubule compared to other BAR proteins [46]. This might explain the sequential necessity of BAR and F-BAR proteins during membrane tubulation [25, 26]. F-BAR proteins demonstrate diverse activities, with some functioning also as a recruiter of phosphatase, tyrosine kinase, or regulator of nitric oxidase synthase. At the C-terminal region, F-BAR domain proteins contain combinations of SH2, tyrosine kinase, Rho GTPase regulatory domains, and SH3 domain. Although the role of F-BAR proteins in membrane invagination has been more heavily emphasized, F-BAR proteins can also participate in the formation of protrusion processes such as filopodia [16, 49].

Role in membrane remodeling and cytoskeletal reorganizatioN

Several BAR proteins possess a SH3 domain through which they almost exclusively interact with (N)WASP and/or dynamins. Both BAR and F-BAR proteins activate actin polymerization via WASP (found exclusive in hematopoietic tissues) or N-WASP (found in non-hematopoietic tissues). This is the case for TOCA-1, FBP17, and Amphyiphysin [24, 28, 50, 51]. BAR-mediated activation of (N)WASP proteins contribute to membrane invagination, vesicle formation, and endocytosis. Dynamins are GTPases that pinch off endocytic vesicles from the plasma membrane. Other proline-rich proteins that interact with BAR SH3 domains include synaptojanin, a lipid phosphatase [52], RhoGAP interacting with CIP4 homologs-1 (RICH-1) [53], and a GTP exchange factor for Rab5 [54].

In particular, F-BAR proteins remodel the plasma membrane and the cytoskeleton in a wide range of organisms and tissue types. The yeast F-BAR proteins cdc15p and Bzzp were found to promote actin polymerization in two different zones along invaginating tubules [55]. Drosophila CIP4/TOCA-1 has been shown to promote membrane invagination then vesicle scission by recruiting dynamin to the vesicle neck [56]. In lamprey cells, the syndapins (also known as the PACSINs) promote vesicle recycling, and their inhibition causes massive accumulation of invaginations and cisternae [57]. TOCA-1 induces filopodia and vesicle formation in N1E115 neuroblastoma cells [49]. In MDA-MB 231 breast cancer cells, CIP4 was found to regulate the formation of invadopodia [58, 59]. Conversely in other studies, PACSIN1 induces dendrite and filopodia formation [15], and PACSIN2 sculpts the plasma membrane of the caveolae [60]. In hippocampal neurons, the F-BAR protein Gas7 enhances protrusion formation [61].

BAR proteins in cancer

Evidence has been accumulating to suggest roles for several BAR proteins in cancer. The amphiphysin-related Bin1 (bridging integrator 1) contributes to Myc and Raf pathways of apoptosis and senescence [8]. One isoform of Bin1 acts as a tumor suppressor by inhibiting c-Myc. Low levels of Bin1 correlate with resistance to platinum by blocking the catalytic activity of poly (ADP-ribose) polymerase 1 [62]. Loss of Bin1 in mosaic mice was associated with overall organ tissue inflammation and lung and liver carcinomas. Also, Bin1 supports T cell-mediated immune surveillance against tumors by restricting the transcription of indoleamine 2,3 dioxygenase, a potent T cell repressor often overexpressed in human tumors [63]. Deletion of Bin3 was also associated with increased lymphomas in aging animals [8].

The properties of remodeling membrane and cytoskeleton make BAR proteins good candidates for promoting epithelial-mesenchymal transition in tumor invasion and metastasis. The F-BAR proteins CIP4 and FBP17 have been implicated in the formation of invadopodia by invasive breast and bladder cancer cells [58, 64]. Invadopodia are finger-like projections supported by actin bundles, and are related to podosomes (**Figure 2**). In the study by Pichot, high levels of CIP4 correlated with the strongly invasive breast cancer cell line MDA-MB 231, with lower levels found in less invasive cell lines such as MCF-7. CIP4 expression promoted breast cancer cell invasion and invadopodia formation through the activation of N-WASP. Also, overexpression of CIP4 in a pancreatic cell line MiaPaCa2 opposed the inhibitory effect of ArgPB2 on cancer cell migration [65].

Through mechanisms poorly understood, CIP4 may mediate chemosensitivity. In a breast cancer cell line, MDA-MB-453, CIP4 over-expression conferred an increased sensitivity to doxorubicin [66]. One mechanism might lie in CIP4's effects on gene expression. Levels of CIP4 influenced methylation patterns in different types of

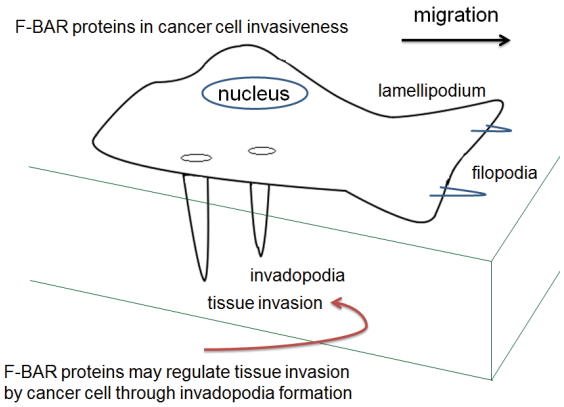

Figure 2. F-BAR proteins in cancer cell invasiveness. Cancer cells invade tissues by undergoing epithelial-mesenchymal transition. One of the first steps for invasion is membrane-cytoskeletal rermodeling (for example,e formation of lamellipodia and filopodia). F-BAR proteins can drive these processes either directly (CIP4 and invadopodia formation) or indirectly (PACSINs and Rac1 activity, which control elements in lamellipodia formation).

human cancer specimens. The CIP4 promoter itself was hypomethylated in CP70 ovarian cancer cells, moderately methylated in MCF7 and MDA-MB231 breast cancer cells and HepG2 liver cancer cells and hypermethylated in IMR-32 (neuroblastoma) and U87 (glioma) brain cancer cells. Overexpression of CIP4 was suppressive to CP70 ovarian cancer cells but promoted tumorigenesis in IMR-32 neuroblastoma cells. CIP4 had different effects, induction versus suppression, of colony formation or tumorigenesis, depending upon the type of tissue giving rise to the tumor [67].

I-BAR proteins, such as Missing-in-Metastasis, have also been implicated in cancer. Missing-in Metastasis gene is present in normal tissues, but missing in several metastatic cell lines [68]. Down-regulated in progressive bladder carcinomas and poorly expressed in transitional cell carcinoma, it is normally found in transitional epithelium [69]. Missing-In-Metastasis has thus been proposed as a suppressor of metastasis gene in bladder cancer [68, 69].

F-BAR proteins in blood disorders

Through their effects on membrane-cytoskeleton remodeling, the F-BAR proteins found to affect immune cell function. An alternative-spliced form of CIP4, (Felic or CIP4b), localizes to the phagocytic cup of the RAW murine macrophage cell line [70]. In the human monocytic THP-1 cell line, FBP17 form podosomes and phagocytic cups through the recruitment of WASP, WIP and dynamin-2 [71]. In mast cells, the tyrosine kinase Fes regulates degranulation through membrane localization via its F-BAR domain prior to Fc epsilon RI activation [72]. CIP4-deficient T lymphocytes was associated with impaired T-dependent antibody response, impaired contact hypersensitivity and defective adhesion to immobilized VCAM1 and ICAM1 in endothelial cells. CIP4$^{-/-}$ T cells had impaired transendothelial migration [73].

PSTPIP1 (Proline-Serine-Threonine-Phosphatase -Interacting Protein 1) has been known to work at the immune synapse by regulating actin organization [74]. This protein also recruits PTP-PEST to the immune synapse where it negatively regulates the activation of T cells by antigen. Point mutations involved in PSTPIP1 and its family member, PSTPIP2, are known to be involved in autoinflammatory diseases. Point mutations of PSTPIP1 in humans are found in PAPA syndrome (pyogenic sterile arthritis, pyoderma gangrenosum and acne), where there is severely reduced binding between the mutant protein and PTP-PEST [75]. Another example of inflammatory disease can be found in mice possessing a point mutation in the MAYP/PSTPIP2 protein [76-78]. These mice exhibit a phenotype similar to chronic recurrent multifocal osteomyelitis, with osteolysis and necrosis in paws of the ears.

More recently, a role for F-BAR proteins in platelet biogenesis has been established in mouse models deficient for CIP4 [79, 80] and PACSIN2 [81]. Platelet biogenesis requires a tremendous amount of highly-coordinated membrane and cytoskeleton remodeling. They are small, anucleated blood cells arising from specialized cells from the bone marrow, which are called megakaryocytes. Progress in imaging has allowed visualization of proplatelet buds and tips arising from the megakaryocytes and where platelets assemble [82]. Proplatelets elongate in a microtubule-driven fashion and platelets are then released form the tips of proplatelets and preplatelets into the blood circulation [83-85]. The F-BAR proteins interact with WASP directly or indirectly by affecting the WASP-WIP complex [71]. The gene encoding WASP is defective in the X-linked congenital thrombocytopenia, Wiskott-Aldrich Syndrome. CIP4 contributes to

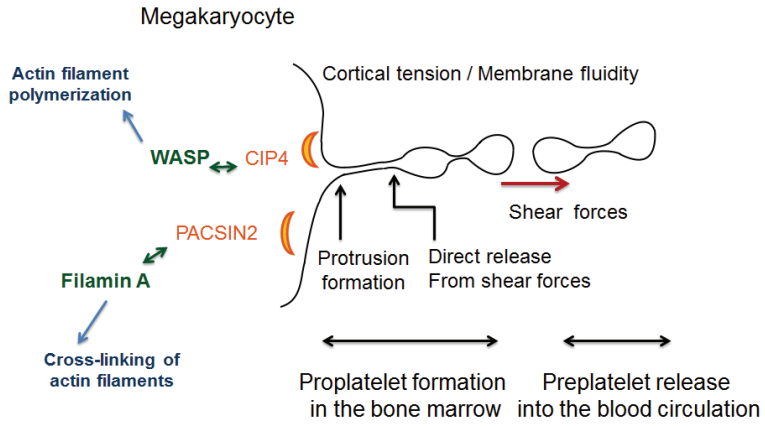

Figure 3. Hypothetic roles of F-BAR proteins in thrombocytopenia. Preliminary studies suggest that F-BAR proteins CIP4 and PACSIN2 contribute to platelet biogenesis. Blood platelets arise from megakaryocytes. Megakaryocytes undergo elongation of plasma membrane to form protrusions called proplatelets into the bone marrow sinusoid vessels [82, 85, 97, 98]. When exposed to shear forces form the blood flow, proplatelets release preplatelets, then platelets, into the circulation [85, 99]. PACSIN2 interacts with filamin A, which may stabilize an intracellular network (Jónsson et al unpublished results). For CIP4, our working hypothesis is that CIP4 modulates plasma membrane fluidity and cortical actin tension (Chen et al, unpublished results).

membrane deformation as well as promoting local actin polymerization through its recruitment of WASP [86]. Altogether, these effects promote efficient proplatelet formation (**Figure 3**). PACSIN2 appears to interact with filamin A, which supports the platelet intracellular membrane system.

BAR proteins and other human diseases

BAR proteins can be associated with human disease, primarily neurologic, such as DNMBP (Dynamin-Binding Protein) in Alzheimer's disease [87], amphiphysin-2 in centronuclear myopathy [13], and oligophrenin in mental retardation/cerebellar hypoplasia [88, 89]. MEGAP/srGAP3/WRP which possesses an inverse F-BAR domain and is known to associate with WAVE,has been implicated in 3p- syndrome and mental retardation [90]. Other examples where BAR proteins may play a role in disease include IRS/p53 in Tourette syndrome [91] and ICA69 as an autoantigen in diabetes mellitus [92-94].

Conclusions

BAR proteins constitute an important group with multiple roles in membrane and cytoskeletal reorganization. The interactions between numerous BAR proteins and either (N)-WASP protein or dynamins promote diverse biological processes such as tubulation, endocytosis, and vesicle trafficking. However, the precise spatial-temporal orchestration is unclear for most of the molecules. Correlation of BAR proteins with diseases underscores the need to further investigate this area in cell biology and biochemistry.

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