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SnapShot: Membrane Curvature Sensors and Generators

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Cells and intracellular organelles are enclosed by bilayer lipid membranes, whose curvatures define their shape. Generation of bilayer curvature is critical for organelle biogenesis and to mediate vectorial transport from one membrane to another via vesicular or tubular intermediates. Membrane curvature can be driven by lipid perturbations that create asymmetry in the two leaflets of the bilayer, by bilayer binding and/or penetrating proteins, or by forces applied to membranes by the cytoskeleton. This SnapShot provides an overview of the mechanisms through which these proteins generate and/or sense curvature. These two properties are tightly interconnected. Proteins that initiate curvature by inserting a wedge in the bilayer (for example, amphipathic helices and hydrophobic loops) will bind preferentially to a precurved bilayer, where bending has created a gap in lipid packing. Likewise, proteins that function primarily as curved scaffolds generally assemble into polymers that propagate curvature, and their binding to the bilayer and their polymerization are both facilitated by a precurved surface. In some proteins, both scaffold mechanisms and wedge-based mechanisms cooperate. Major mechanisms of protein-driven membrane deformation are listed below. Examples given refer to structures and schematic cartoons shown in the figure.

Amphipathic Helices

Amphipathic helices, which include the so-called ALPS motif, are α-helical lipid binding motifs with segregation of hydrophobic and polar amino acids on opposite sides of the helix. These helices, which are arranged parallel to the bilayer, partially penetrate it via their hydrophobic face and are well suited for membrane deformation and curvature sensing. Examples of proteins that contain amphipathic helices include:

Epsin

An adaptor protein in clathrin-mediated endocytosis. Amphipathic helix residues = aa 1–17 in human epsin 1.

Synuclein

A synaptic vesicle-associated protein that binds synaptic vesicles through its N-terminal amphipathic helix. Amphipathic helix residues = aa 9–41 in human α-synuclein.

Sar1

Small GTPase that initiates assembly of the COPII coat implicated in vesicle budding from the ER. Amphipathic helix residues = aa 1–25 in human Sar1B.

Arf1

Small GTPase that initiates assembly of the COPI coat and of the clathrin coat in the Golgi complex. Amphipathic helix residues = aa 1–18 in human Arf1.

Arf1GAP

GTPase-activating protein (GAP) for Arf1. By promoting Arf1-mediated GTP hydrolysis, Arf1GAP facilitates dissociation of coat proteins from Golgi-derived membranes. Amphipathic helix residues = aa 199–223 in human Arf1GAP.

Endophilin

BAR-domain-containing protein implicated in tubular membrane deformation in endocytosis. Amphipathic helix residues = aa 1–21 in human endophilin A3.

Loop Insertion

Some proteins contain a short peptide loop with hydrophobic residues that inserts into one leaflet of the lipid bilayer. Examples of proteins with loop insertion include:

Synaptotagmin 1

Synaptic vesicle protein. The Ca^{2+}-dependent interaction of its cytosolic C2 domain region with the bilayer regulates exocytosis. Its induction of curvature in the plasma membrane via its binding “in trans” to this membrane was proposed to facilitate fusion.

EHD2

ATPase involved in tubular membrane deformation in the endocytic pathway.

Pacsin1

F-BAR-domain-containing protein involved in the endocytic pathway.

Membrane Embedding

In some proteins, a stretch of hydrophobic residues forms a hairpin embedded in the bilayer rather than a *trans*-membrane span. The partial penetration of the hairpin in the bilayer, deeper than in the case of loop insertion, is thought to create asymmetry in the bilayer. Some of these proteins may further oligomerize into scaffolds to facilitate membrane deformation. Examples include:

Reticulons

Endoplasmic reticulum (ER) proteins involved in the generation of the tubular structure of the ER.

Flotillin

Scaffold protein involved in a clathrin-independent endocytic pathway.

Caveolin

Key component of caveolae.

Classic Coats

Classic coats are polymeric structures that form a cage around a membrane bud or vesicle. Components of the coats generate and/or adapt to membrane curvature both via direct interactions with the cargo proteins and the bilayer and by assembling into a curved polymer. In some cases, the assembly of these coats is generally initiated by a small GTPase that has curvature-generating/sensing properties (amphipatic helix). The small GTPase helps recruit the adaptor layer. The adaptor layer may contain curved surfaces or amphipatic

helices. The outer layer is represented by elongated proteins that assemble to form a cage-like structure.

COP II Coat

Regulates vesicular transport from the ER to the Golgi complex.

COPI Coat

Regulates vesicular transport from the Golgi complex to the ER and between Golgi cisternae.

Clathrin Coat

Regulates vesicle budding from the *trans*-Golgi, the plasma membrane, and the endosomal compartment.

Caveolar Coat

The high curvature of these membrane buds had been assigned primarily to caveolin (see above, Membrane Embedding). More recently, cavin, a peripheral membrane protein that assembles at their surface, was shown to have a critical role in their formation and stability.

Scaffolds with a Curved Membrane Interface

Some proteins bind the bilayer via a curved surface. However, polymerization of these proteins, generally into helical structures, helps to impose and propagate curvature. For other proteins, the curved interface is generated by their polymerization into rings or helices.

BAR Domain Superfamily

BAR (Bin, amphiphysin and Rvs161/167) domains are α-helical coiled-coil structures that dimerize into protein modules to generate a positive charged surface with intrinsic curvature. Based on their structures, they can be subgrouped in different families with different intrinsic curvature of their bilayer binding surface: shallow and narrow concave curvature in F-BAR and BAR (including N-BAR), respectively, and convex curvature in I-BAR (inverse-BAR). BAR domains are often closely associated with additional membrane binding modules, such as PH domains and PX domains, which enhance membrane affinity. In N-BAR domains, an amphipathic N-terminal helix facilitates bilayer curvature sensing and induction. Examples of BAR proteins include:

Amphiphysin

N-BAR-domain-containing accessory factor in endocytosis.

LSP1

One of the main structural components of the eisosomes; groove-like invaginations of the plasma membrane in fungi.

Endophilin

N-BAR-domain containing endocytic protein (see Amphipathic Helices). Cryo-EM analysis of an endophilin polymer revealed that amphipathic helices can interact in *trans* to stabilize the BAR domain polymer (see figure).

APPL1

Protein of early endosomes with traffic and signaling functions.

SNX9

PX-BAR-domain-containing protein implicated in endocytosis and actin regulation.

FBP17/TOCA1/CIP4 and Pacsin1

F-BAR domain proteins, which may coordinate endocytic invaginations with reorganization of the actin cytoskeleton.

FCHO2

F-BAR-domain-containing protein involved in an early step of clathrin-mediated endocytosis.

IRSp53

I-BAR protein thought to coordinate actin cytoskeleton rearrangement and filopodia formation.

ESCRTIII

Subcomplex of the ESCRT system that is implicated in the formation of intraluminal vesicles of multivesicular bodies. CHMP3, a core component of ESCRTIII that mediates bud invagination and vesicle fission, has a convex bilayer binding surface and further undergoes helical polymerization.

ATPases and GTPases

Dynamin

GTPase implicated in endocytic vesicle fission that oligomerizes into spirals defining a curved membrane binding interface. Its GTPase activity, which is dependent on its assembly, leads to vesicle fission

EHD2

ATPase involved in the endocytic pathway, which oligomerizes into rings. Its bilayer binding interface (see loop insertion) and its oligomerization define its curvature generating/sensing properties.

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Helical wheel diagrams were made with Heliquest. Molecular representations were rendered with PyMOL (The PyMOL Molecular Graphics System, Version 1.5.0.1). PDB codes for structures are as follows: 2QPT (EHD1), 3FRT (CHMP3), 1K5W (C2 of synaptotagmin 1), 3SNH (dynamin 1), 1Y2O (I-BAR domain of IRSp53), 3HAH (F-BAR domain of Pacsin1), 2Z0V (N-BAR domain of endophilin A3), 2RAK (PX-BAR domain of SNX9), 2ELB (BAR-PH domain of APPL1), 2EFK (F-BAR domain of CIP4), 2V0O (F-BAR domain of FCHO2), 2C08 (N-BAR domain of endophilin A1), 3PLT (BAR domain of LSP), and 1URU (N-BAR domain of Amphiphysin).

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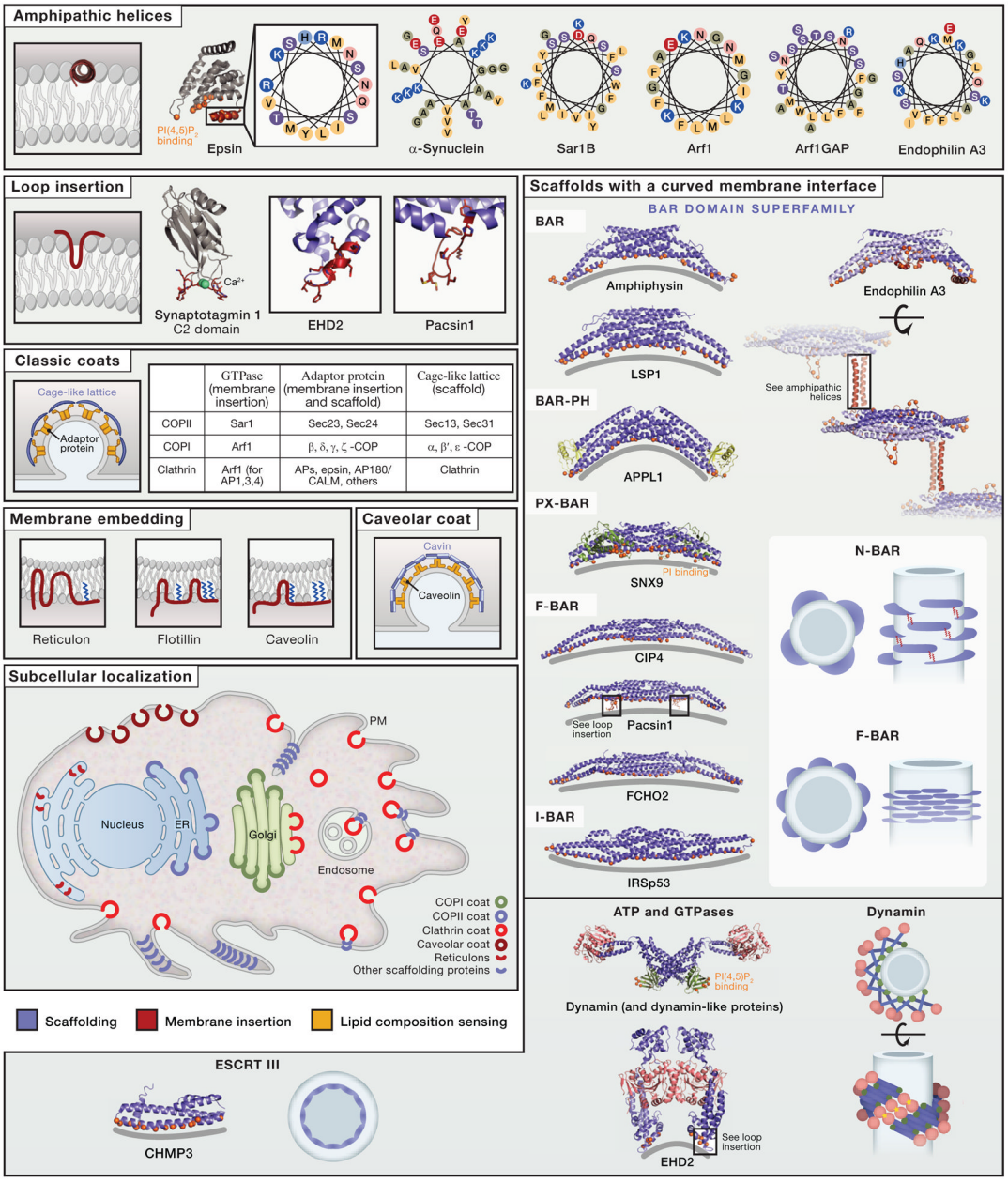

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