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Review Article

Integrating Fundamental Biology and Translational Potential: Advancing the Frontiers of Membrane Biology through Dynamic Modulation of Cellular Membranes Proteins

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Abstract:

Cellular membranes are highly dynamic structures that undergo constant remodeling to support a variety of cellular processes, including signaling, endocytosis, vesicle trafficking, and cell migration. This dynamic behavior is largely regulated by the interactions between phospholipids, which form the lipid bilayer, and membrane-deforming proteins, which induce changes in membrane curvature and shape. Phospholipids such as phosphatidylcholine, phosphatidylinositol, and phosphatidylserine provide structural stability to the membrane and act as signaling molecules that modulate membrane dynamics. Membrane-deforming proteins, including BAR-domain proteins (Bin/Amphiphysin/Rvs domain), Clathrin, and dynamin, interact with phospholipids to bend, pinch, or remodel the membrane, facilitating vesicle formation and endocytosis. The coordinated action between phospholipids and membrane-deforming proteins is crucial for cellular functions such as membrane repair, signal transduction, and cell motility. This review explores the roles of these two key components in the dynamic modulation of cellular membranes and their importance in maintaining cellular homeostasis. Understanding these interactions may provide insights into diseases associated with membrane dysfunction, offering potential therapeutic targets.

Keywords: Cellular membranes, Phospholipids, Membrane-deforming proteins, BAR-domain proteins, Clathrin, dynamin, Membrane dynamics, Vesicle trafficking, Signal transduction.

1. Introduction

Cell membranes primarily comprise a lipid bilayer, providing a flexible and semi-permeable structure. Phospholipids, the major component of this bilayer, are essential for the membrane's integrity, fluidity, and overall function. However, cellular membranes are not static; they undergo constant remodeling to facilitate vesicle formation, endocytosis, and membrane trafficking (1). This dynamic regulation is largely driven by the actions of membrane-deforming proteins that interact with lipids to alter the curvature, shape, and mechanical properties of the membrane. This interplay between phospholipids and membrane-deforming proteins is essential for cellular processes such as signaling, transport, and even cell division (2). Cellular membranes are fundamental to the structure and function of cells, providing a barrier that separates the internal environment from the external one while facilitating essential processes such as signaling, transport, and cell division (3). The dynamic properties of cellular membranes are not merely passive but are actively regulated by phospholipids and membrane-deforming proteins. This review explores how these two components interact to shape and remodel cellular membranes, influencing cellular function and morphology (4).

2. Phospholipids in Membrane Modulation

2.1. Structure and Function of Phospholipids

Phospholipids are amphipathic molecules, with hydrophilic (water-attracting) head groups and hydrophobic (water-repelling) tails (5). The interaction between the hydrophilic heads and water molecules leads to the formation of bilayers, where the hydrophobic tails are shielded from the aqueous environment.

2.2. Classes of Phospholipids

Different classes of phospholipids such as phosphatidylcholine (PC), phosphatidylethanol-amine (PE), phosphatidylserine (PS), and phosphatidylinositol (PI) contribute to membrane structure and function in diverse ways.

2.3. Lipid Mobility and Domain Formation

Phospholipids undergo rapid interconversion and lateral diffusion within the membrane. The composition of lipids in the membrane can influence the formation of specialized domains, such as lipid rafts, involved in protein sorting, signal transduction, and membrane trafficking (3).

3. Membrane-Deforming Proteins

Membrane-deforming proteins are key players in the dynamic modulation of cellular membranes. Through their interactions with phospholipids, these proteins can induce curvature and alter the shape of the lipid bilayer. Various classes of membrane-deforming proteins have been identified, including BAR-domain proteins, clathrin, dynamin, and certain GTPases (8).

3.1. BAR Domain Proteins

The BAR (Bin/Amphiphysin/Rvs) superfamily of proteins is one of the most well-studied groups of membrane-deforming proteins. These proteins contain a characteristic crescent-shaped domain that binds to and bends the lipid bilayer (9). BAR-domain proteins can promote membrane fission (e.g., during vesicle budding) or membrane fusion (e.g., during endocytosis) by curving the membrane. Additionally, BAR proteins often recruit other proteins that further deform or stabilize the membrane curvature (10).

3.2. Clathrin and Dynamin

Clathrin-mediated endocytosis is a process in which cells internalize extracellular material by forming Clathrin-coated vesicles (11). Clathrin itself forms a lattice-like structure that shapes the membrane into a highly curved vesicle. The protein dynamin plays a critical role in scission, the process by which the vesicle is pinched off from the membrane. Dynamin uses energy from GTP hydrolysis to constrict the neck of the vesicle, facilitating membrane separation (12).

3.3. GTPases

Small GTPases such as Rho, Ras, and Arf are involved in membrane remodeling during processes like actin polymerization, vesicle trafficking, and cell migration (13). These GTPases regulate the function of other membrane-associated proteins, thereby controlling membrane curvature and dynamics. For instance, Arf1 is involved in forming COPI-coated vesicles, which are important for retrograde transport within the cell (14).

4. Interaction Between Phospholipids and Membrane-Deforming Proteins

The interaction between phospholipids and membrane-deforming proteins is highly dynamic. Phospholipids provide the structural foundation for membrane deformation and actively participate in the process. For example, certain lipids like PIP2 can act as signaling molecules that recruit membrane-deforming proteins to specific membrane regions. These lipids can induce conformational changes in the membrane-deforming proteins, allowing them to bind more effectively and promote membrane curvature (15).

Conversely, membrane-deforming proteins can alter the local concentration and distribution of phospholipids. For example, proteins like phospholipase D can hydrolyze specific phospholipids, such as phosphatidylcholine, to produce molecules like phosphatidic acid that modulate membrane curvature. Additionally, the recruitment of specific proteins to lipid rafts or specialized lipid domains can further modulate membrane function (16).

5. Physiological Relevance and Cellular Processes

The dynamic modulation of cellular membranes by phospholipids and membrane-deforming proteins plays a central role in several key cellular processes:

5.1. Vesicle Formation and Trafficking

Membrane-deforming proteins such as clathrin and dynamin are required for the formation and scission of vesicles, while BAR-domain proteins assist in shaping the membrane (17).

5.2. Cell Migration

Membrane remodeling is critical for cell migration, facilitated by the concerted action of membrane-deforming proteins and phospholipids (18).

5.3. Membrane Repair

Membrane-deforming proteins are involved in cellular repair processes following mechanical injury (19).

5.4. Signal Transduction

Membrane curvature and lipid composition influence signaling pathways, such as those involving PIP2 (20).

6. Fundamental Mechanisms of Membrane Curvature Formation

Membrane curvature is a dynamic and essential feature of cellular membranes, and several mechanisms can drive its formation. These can be grouped into three main categories: lipid metabolism, protein scaffolding, and protein insertion or interaction. The proteins involved in these processes are summarized in **Table 1**.

6.1. Lipid Metabolism

The shape of individual lipid molecules—whether cylindrical, conical, or inverted conical—plays a key role in determining membrane curvature **(Figure 1A).** An increased presence of lipids with conical or inverted conical shapes often promotes membrane deformation. This lipid enrichment can be achieved through changes in lipid metabolism, which includes the synthesis and transport of new lipids to the membrane. Enzymes can also modify lipids by adding or altering their head groups, which affects their shape and the overall membrane curvature.

For example, phosphoinositides (phosphorylated forms of phosphoinositides) have relatively large head groups, which can induce local membrane curvature. However, the low concentration of phosphoinositides in the plasma membrane suggests that they are not the main drivers of global membrane curvature. Instead, phosphoinositides are likely to affect local membrane curvature at specialized sites, such as clathrin-coated pits, caveolae, and near membrane receptors.

Another lipid-based mechanism for curvature involves the hydrolysis of the acyl chain in phospholipids. This conversion can change the shape of the lipid from conical to inverted conical, promoting curvature. For example, phosphatidic acid (PA), which has a conical shape, can be converted to lysophosphatidic acid (LPA), which has an inverted conical shape, thus inducing membrane curvature. Although early studies suggested that the enzyme endophilin could promote membrane deformation through PA hydrolysis, later research revealed that the membrane-deforming activity was primarily due to the BAR domain of endophilin (21).

Table 1: summarizing key proteins involved in the fundamental mechanisms of membrane curvature formation, along with their mechanisms, functions, and relevant references:

Protein	Mechanism	Function in Membrane Curvature	Example Processes	References
Clathrin	Protein scaffolding	Forms a lattice-like structure that aids in the formation of clathrin-coated vesicles.	Endocytosis, vesicle formation	(21)
Dynamin	Membrane scission	GTPase that constricts and pinches off vesicles from the membrane.	Vesicle scission during endocytosis	(22)
BAR-domain proteins	Protein scaffolding and membrane bending	Bind to and bend the membrane, creating curvature via their crescent-shaped structure.	Endocytosis, vesicle trafficking, cell division	(23)
COPI and COPII	Protein scaffolding	Coat proteins that help in vesicle formation for ER-to-Golgi and Golgi-to-ER transport.	Vesicle transport between the ER and Golgi	(24)
Arf GTPases	Protein-mediated curvature induction	Activate COPI and COPII coat complexes by regulating membrane binding and curvature.	Vesicle trafficking, protein sorting	(25)
Endophilin	Lipid metabolism and protein scaffolding	Binds lipids and induces membrane curvature, especially through interaction with phosphatidic acid (PA).	Endocytosis, synaptic vesicle recycling	(23)
Amphiphysin	Protein scaffolding	Binds to the membrane and induces curvature through its BAR domain.	Synaptic vesicle formation, endocytosis	(21)
Caveolin	Protein scaffolding	Forms caveolae structures by oligomerizing to induce membrane curvature.	Caveolae formation, lipid rafts	(26)
ESCRT proteins	Protein scaffolding	Forms a protein complex required for membrane scission during the final stages of endosomal sorting.	Multivesicular body formation, cytokinesis	(27)
Flippases/Floppases	Lipid metabolism	Transport lipids across the membrane bilayer, contributing to membrane asymmetry and curvature.	Membrane lipid organization, apoptosis	(28)
TMEM16F (Scramblase)	Lipid metabolism	Scrambles phospholipids between membrane leaflets, inducing curvature, especially during apoptosis.	Apoptosis, membrane repair	(29)

Additionally, membrane curvature can be influenced by lipid transport mechanisms. Flippases, enzymes that transport lipids between the two layers of the lipid bilayer, contribute to membrane asymmetry during processes like cytokinesis and cell migration. For example, type IV P-type ATPases (P4-ATPases) and CDC50 proteins form complexes that flip phospholipids like phosphatidylserine (PS) and phosphatidyl-ethanolamine (PE) from the inner to the outer leaflet during apoptosis, which can also alter membrane curvature. The transmembrane protein TMEM16F, a lipid scramblase, also plays a role by scrambling membrane phospholipids, leading to PS exposure on the cell surface during apoptosis (30).

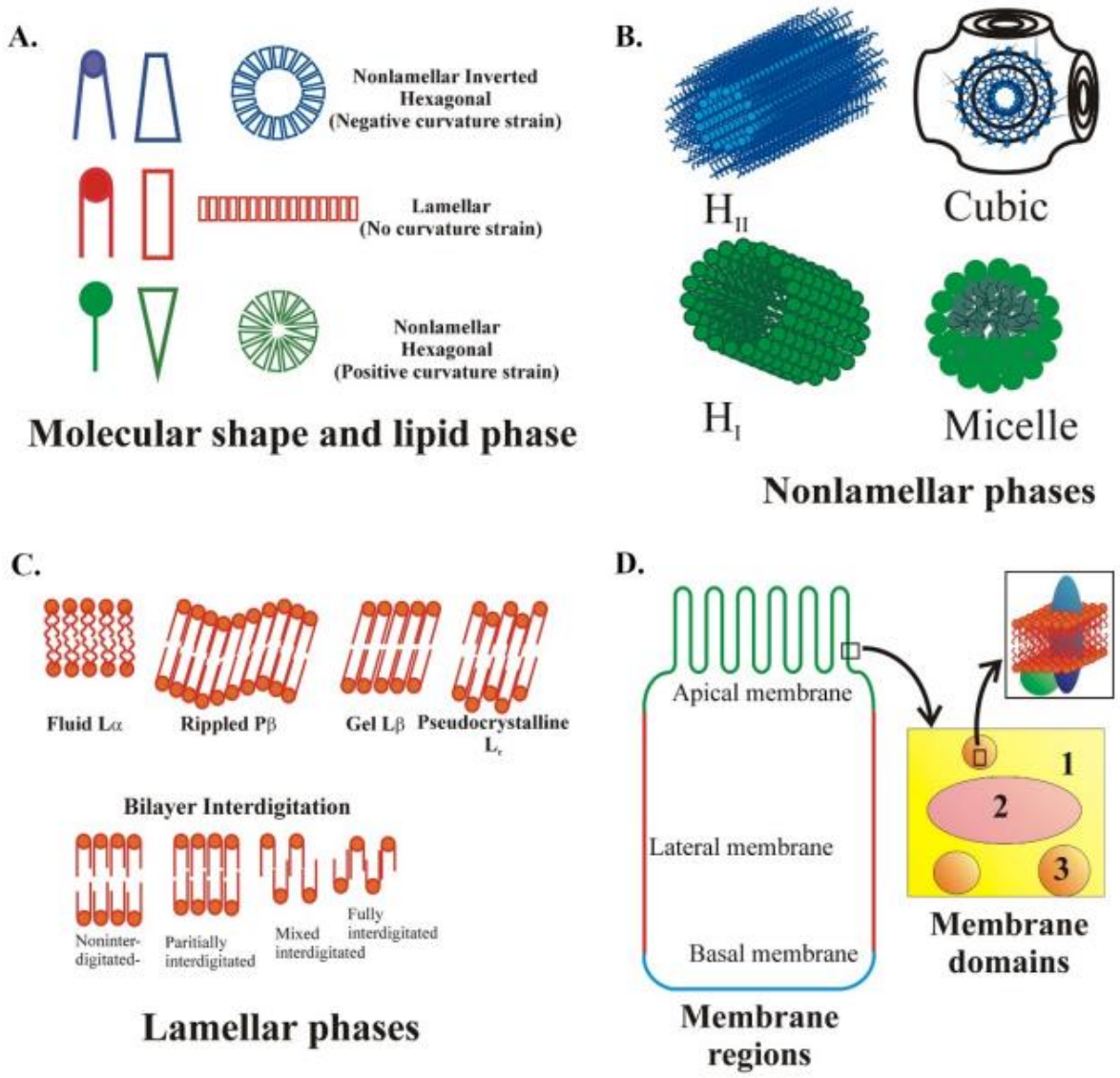

Figure 1. Lipid Shapes and Mechanisms of Membrane Interaction and Deformation (A) Molecular shape, (B) nonlamellar phases, (C) lamellar phases, and (D) polarized cells. Adapted from (31)

A: Lipid molecules can be classified by shape into three main types: cylindrical, conical, and inverted conical. Each lipid type naturally forms distinct membrane structures on its own, but biological membranes—such as lipid bilayers—contain a mix of these lipid types. Despite this mixture, biological membranes generally appear flat on a larger scale, though at the submicron level, structures like clathrin-coated pits introduce significant curvature.

B: Protein domains that bind to and recognize lipids are categorized by their interaction mechanisms: basic charge-based binding that does not differentiate lipid species, specific recognition of lipid types based on protein structure, membrane recognition, and bending facilitated by insertion of an amphipathic helix or hydrophobic loop, and structural deformation of membranes driven by protein domains, such as BAR domains, which sculpt membrane curvature (31).

6.2. Indirect Protein Scaffolding

Membrane deformation can also occur through protein scaffolding mechanisms, where proteins do not directly bind to the membrane but help shape the membrane by forming scaffolds or lattices. One well-known example is the clathrin-coated pit, which is involved in clathrin-mediated endocytosis. Clathrin is not a membrane-binding protein; it is attached to the membrane via adaptor proteins (APs) and cargo proteins. The assembly of clathrin into a rigid lattice structure facilitates the budding and scission of clathrin-coated vesicles from the plasma membrane (31).

Similarly, the COPI and COPII coat complexes are involved in vesicle transport between the endoplasmic reticulum (ER) and the Golgi apparatus. While some components of these complexes directly bind to the membrane, others, such as the GTPase Arf, play crucial roles in the assembly of the coat on the membrane, which promotes membrane curvature (24).

In some cases, membrane deformation is driven not by direct membrane-binding proteins, but by the assembly of proteins on the membrane in a way that promotes bending. This process, known as protein "crowding," suggests that the physical crowding of proteins on the membrane can generate curvature. For example, the assembly of adaptor protein (AP) complexes at clathrin-coated pits may contribute to membrane bending through crowding and protein assembly. However, the role of protein crowding in membrane curvature in vivo is still under investigation, and more research is needed to fully understand it (32)

6.3. Regulation of BAR domain superfamily:

The BAR domain superfamily is unique in its structural characteristics and interactions with membrane curvature. Understanding its regulation is crucial due to its various biological functions. Many cytosolic proteins are activated upon phosphorylation or charge addition, which can impact their membrane association (33).

For instance, the BAR domains of ACAP4 have been reported to be activated by phosphorylation during membrane association, depending on epidermal growth factor (EGF) stimulation. However, the negative charge may enhance repulsion from anionic lipids in the membrane. Drosophila syndapin/PACSIN is also phosphorylated, which inactivates its membrane tubulation ability. Mammalian PACSIN1 and PACSIN2 are similarly phosphorylated, leading to defective neuronal morphologies and functions (34).

7. BAR Proteins and Disease

The BAR protein family is essential in forming delicate membrane structures like protrusions, filopodia, lamellipodia, and endocytotic invaginations. Dysfunction in these proteins is often linked to various diseases.

7.1. Cancer

Mutations in BAR proteins such as Bin1 have been linked to cancer, influencing cell signaling pathways (35, 36).

7.2. Immune System Disorders

F-BAR proteins like CIP4 and PSTPIP1 are crucial for immune cell function, with mutations linked to disorders such as PAPA syndrome (37–38).

7.3. Muscle Disorders

BAR proteins are vital for muscle function, with mutations causing conditions like centronuclear myopathy (39&40).

8. Perspective on the Disease Treatments

The role of membrane curvature and membrane proteins is pivotal in disease progression, particularly in viral infections and neurodegenerative disorders:

8.1. Viral Infections

Enveloped viruses like influenza, Ebola, dengue, HIV, and HBV rely on membrane curvature changes for key processes such as fusion, budding, replication, and immune evasion. Viral proteins, such as hemagglutinin (influenza), viral protein 40 (Ebola), non-structural protein 4A (dengue), and Nef (HIV), manipulate membrane curvature to facilitate their life cycles. Membrane dynamics also affect mitochondrial membrane permeabilization and chronic liver i8.

8.2. Neurodegenerative Disorders

In Alzheimer's disease, amyloid β peptides interact with membranes to form toxic aggregates. High membrane curvature promotes fibril formation, accelerating amyloid aggregation, while lower curvature results in shorter fibrils and amorphous aggregates (42).

The focus on phospholipids and membrane-deforming proteins as potential drug targets is forward-looking, suggesting innovative therapeutic avenues for diseases linked to membrane dysfunction.

Overall, these insights underscore the importance of membrane-protein interactions in disease mechanisms and suggest potential avenues for therapeutic interventions targeting these processes.

All the above give a holistic view of membrane dynamics, emphasizing the interplay between lipids and proteins while linking molecular

mechanisms to cellular functions and diseases. This dual focus on fundamental biology and translational potential marks its novelty and significance in advancing the field of membrane biology.

9. Summary and Outlook

The dynamic modulation of cellular membranes by phospholipids and membrane-deforming proteins is essential for maintaining cellular homeostasis and enabling critical processes such as vesicle trafficking, cell migration, and signal transduction. The interaction between these two components is highly regulated, allowing cells to respond rapidly to internal and external cues. Understanding how phospholipids and membrane-deforming proteins work together will provide deeper insights into cellular behavior and may offer new therapeutic targets for diseases involving membrane dysfunction.

These findings emphasize the dynamic interaction between membrane curvature and proteins within living systems. Additionally, the review discusses how these interactions influence disease progression and help maintain typical membrane structures to prevent disease.

Looking forward, further research is essential to deepen our understanding of how the relationship between membrane proteins and curvature can inform disease treatments. Emerging evidence suggests that the curvature-sensing properties of membrane proteins hold potential for therapeutic applications, such as enhancing cancer immunotherapy by disrupting tumor-derived exosomes. However, our understanding of the role of these interactions in the pathogenesis of various diseases remains incomplete, limiting their application in developing effective therapies. Future studies should focus on unraveling the specific contributions of membrane curvature and protein interactions in disease mechanisms, paving the way for innovative treatment strategies.

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Abbreviations

BAR-domain: Bin/Amphiphysin/Rvs domain

PC: Phosphatidylcholine

PE: Phosphatidylethanolamine

PS: Phosphatidylserine

PI: Phosphatidylinositol

PIP2: Phosphatidylinositol 4,5-bisphosphate

GTPase: Guanosine triphosphatase

COPI: Coat Protein Complex I

COPII: Coat Protein Complex II

Arf: ADP-ribosylation factor

Rho: Ras homolog gene family

Ras: Rat sarcoma virus oncogene

ESCRT: Endosomal Sorting Complex Required for Transport

AP: Adaptor Protein

EGF: Epidermal Growth Factor

N-WASP: Neural Wiskott–Aldrich Syndrome Protein

CRIB: Cdc42/Rac Interactive Binding motif

VCA: Verprolin, Central, Acidic domains

PI, P2: Phosphatidylinositol bisphosphate

Rac: Ras-related C3 botulinum toxin substrate

PSTPIP1: Proline-Serine-Threonine Phosphatase Interacting Protein 1

PSTPIP2: Proline-Serine-Threonine Phosphatase Interacting Protein 2

SH3: Src Homology 3 domain

PTP-PEST: Protein Tyrosine Phosphatase - Proline, Glutamic acid, Serine, Threonine

VCAM1: Vascular Cell Adhesion Molecule 1

ICAM1: Intercellular Adhesion Molecule 1

PAPA syndrome: Pyogenic Arthritis, Pyoderma gangrenosum, and Acne

F-BAR: Fes/Cip4 Homology-BAR domain

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