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The organisation of the cell membrane: do proteins rule lipids?

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Cell membranes are a complex adaptive system: they are constantly re-organised in response to extra- and intracellular inputs and their local and global structure ultimately determines how, where and when these inputs are processed. This requires a tight coupling of signalling and membranes in localised and specialised compartments. While lipids are essential components of cell membranes, they mostly lack a direct link to the input signals. Here we review how proteins can deform locally membranes, modify and reorganise lipids to form membrane domains and regulate properties like membrane charges and diffusion. From this point-of-view, it appears that proteins play a central role in regulating membrane organisation.

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Introduction

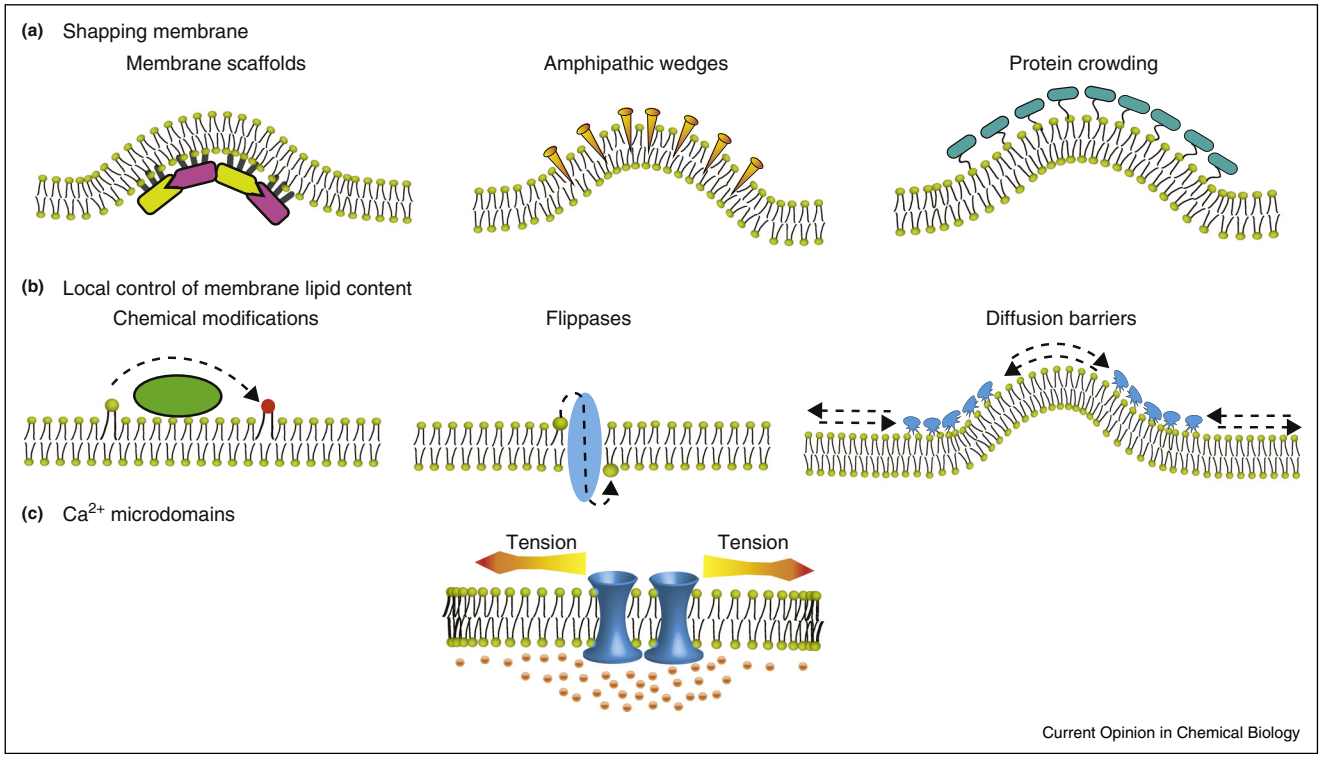
The plasma membrane is a gateway that coordinates extracellular signals with intracellular responses and *vice versa*, links intracellular processes to cell–cell interactions and tissue organisation. Thus, the plasma membrane extends to intracellular endosomes and extracellular vesicles to mediate cell functions such as receptor signalling, presentation of surface proteins and protein secretion [1]. There is overwhelming evidence that the plasma membrane is not a homogenous mixture [2], but how cellular membranes are compartmentalised and which contribution lipids and proteins make to this compartmentalisation is the topic of on-going debate. The reason why membrane domains have attracted so much attention is that membrane organisation conceptualises how cells can actively coordinate processes to adapt and respond to their environment. Upon signalling, cell membranes rearrange in specialised domains, with distinct properties such as composition, charge, curvature or condensation. These domains then act as signalling platforms and coordinate cellular events. While lipids may contribute and determine the plasticity of domain formation, it is proteins that hold the key to *triggering* such membrane re-organisation in an active and regulated manner. Here we focus on how proteins can locally impact on membrane organisation and structure, either by acting on the biophysical properties of cell membranes, for example *via* mechanical forces or by introducing delimited changes in the membrane lipid composition.

Pushing, pulling or bending: proteins that shape membranes

Cellular processes such as endocytosis, exocytosis and signalling require controlled and localised membrane deformation [3••,4]. Although some lipids have intrinsic curvature, localised changes in topography are most likely enforced upon the membranes by specialised proteins. In the following paragraphs, we describe examples of proteins that shape cellular membranes.

The Bin/amphiphysin/Rsv161 (BAR) domain protein superfamily has emerged as one of the main factors that control of membrane bending [5]. Various types of BAR domain proteins can generate a wide range of curvatures. Although they lack a consensus sequence motif, BAR domain proteins typically form homo or hetero dimers that structurally assemble in a curved 'banana' shape. Mechanistically, BAR domain proteins exemplify the two ways peripheral proteins generally induce curvature: 1) by acting as a membrane scaffold and bending the membrane due to their intrinsically curved structure, or 2) by inserting amphipathic wedges and asymmetrically displacing lipids in the membrane leaflet with which they interact (Figure 1A). Consistent with their shape, BAR domain proteins are also membrane curvature sensors and can act as protein scaffolds thanks to SH3 domains. These features give BAR domain proteins not only the ability to enhance pre-existing membrane curvature, but also to recruit other proteins to membrane sites with specific curvature. Notably, several members of the BAR proteins superfamily recruit and activates members of the WASP family to promote actin polymerisation at site of membrane curvature and to generate tubule elongation [6]. By stabilising membranes with high curvature, BAR domain proteins can also inhibit membrane fission [7]. In a mechanism similar to that of BAR domain proteins, Exo70, a protein of the exocyst complex, oligomerizes into scaffolds that generate positive membrane curvature. Exo70, which binds to phosphatidylinositol 4,5-bisphosphate (PIP2), shapes

Figure 1



Local control of membrane shape and composition by proteins. **(A)** Proteins can shape membranes, either by (from left to right) membrane-bound scaffolds imprinting their shape onto the membrane, insertion of amphipathic wedges into one leaflet of the bilayer or through steric pressure generated by the crowding of membrane-bound molecules. **(B)** Proteins locally regulate the lipid composition of cell membranes. From left to right: Membrane-bound enzymes modify the chemical structure of lipids, flippases move lipids from one leaflet to the other, plasmalemmal proteins act as diffusion barriers to create lipid microdomains. **(C)** In response to membrane tension, transient receptor potential ion channels can trigger ion influxes that modify the charge of lipids in a restricted area of the cell membrane.

membrane protrusion that can be actin-free and contribute to the formation of the leading edge in migrating cells [8].

Caveolae are another classical example of membrane organisers and represent distinct invaginations in the plasma membrane shaped by 140–150 caveolins [9]. Caveolin-1 is the best-characterised caveolin member and binds to the inner leaflet of the plasma membrane *via* palmitoylation. The accepted mechanism is that caveolin-1 creates membrane curvature through a putative hairpin domain wedging into the inner leaflet and its ability to oligomerize. Cavins, a family of cytoplasmic proteins, cooperate with caveolins to drive caveolae formation.

Tetraspanins are structural proteins bearing four transmembrane domains and control the formation of membrane tubules [10]. Similarly to BAR domains proteins, they can oligomerize and recruit various proteins to establish functional microdomains. Tetraspanins have been reported to be involved in almost all cell function requiring membrane shape changes. Different members of the tetraspanins family fulfil different membrane shaping function, either favouring (CD81, CD9, CD151) or inhibiting (CD82) membrane extension. It is not yet clear how exactly tetraspanins promote the formation of membrane tubules but evidences point towards their ability to both generate membrane curvature and control actin polymerisation [10,11].

The endosomal sorting complex required for transport (ESCRT) comprises five separate complexes and drives the formation of multivesicular bodies and cell scission in cytokinesis. ESCRT 0, I and II recognise phosphatidylinositol (3,4,5)-trisphosphate (PIP3), form stable assemblies and recruit ESCRT-III, which transiently polymerise to shape the membrane in a mechanism that we just begin to understand [12]. ESCRT-III starts to assemble on the inner leaflets in the form of concentric spirals. Sequential incorporation of ESCRT-III subunits then triggers a switch in these structures from 2-dimensional spirals to 3-dimensional helixes, pushing the membrane and generating a bud, which eventually severs from the plasma membrane [12].