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Opinion Article

Membrane-Mediated Protein Interactions Promoting Membrane Protein Assembly

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DESCRIPTION

A major component of the plasma membrane, i. H. Phospholipids and membrane proteins are known to organize into functional lipid protein domains and super complexes. The active membrane-intrinsic processes that generate membrane organization are unknown. Therefore, to understand membrane protein organization, it is necessary to consider thermodynamic interactions and biophysical determinants of membrane-mediated protein interactions. Here, we used high-speed atomic force microscopy and dynamics and membrane elasticity theory to study the behavior of model membrane proteins during oligomerization and assembly in a controlled lipid environment. Hydrophobic mismatches in membranes were found to modulate oligomerization and assembly energies, as well as 2D organization. Our experimental and theoretical frameworks show how membrane organization arises from Brownian diffusion and minimal physical properties of membrane constituents.

In a modified version of the fluid mosaic model, membranes are not passive mediators, but play an active role in regulating membrane protein function and organization through their physical properties. In contrast, direct experimental investigation of membrane-mediated oligomerization and membrane protein assembly remains challenging.

When the interaction energies between all of the components are of the order of kBT2, her two-dimensional (2D) architecture of the biological membrane degenerates into randomness. In actuality, the membrane proteins that make up cell membranes display a non-random arrangement. Lipid-protein rafts, functional domains, and membrane-protein super complexes have been identified as distinctive markers of biological membrane non-randomness using fluorescence microscopy and biochemical studies. Both the external environment and phospholipids and cholesterol are parts of the membrane in eukaryotic cells. The extracellular matrix and cytoskeleton contribute to non-random membrane organisation. While the membrane is a medium for molecular interactions and its effects can be investigated in a controlled manner, peripheral contacts bind membrane molecules and serve as a lateral diffusion barrier. To our knowledge, there are no known intrinsic membrane-active processes that regulate and localize membrane proteins to membranes.

First, membrane protein interactions can be protein-mediated. That is, two partner molecules either makes direct protein-protein contacts or interact through a third protein. Strong interaction, B. Hydrogen bonding, ionic and dipole interactions occur. Second, membrane-protein interactions are likely to be membrane-mediated, with predominantly hydrophobic amino acid residues on the membrane protein surface exposed to the hydrophobic phospholipid bilayer core. As a result, the strong interactions described above do not occur. In this case, enough energy, i. H. few kBTs are generated from weak hydrophobic interactions between lipids and membrane proteins, and from unique membrane physical properties. Over the past decades, numerous theoretical and computational studies have predicted an important role for membrane mechanics. An interesting aspect of membrane-mediated interactions is their long range, although strong hydrophilic and weak hydrophobic interactions across the cytoplasmic and extracellular domains can coexist. In fact, membrane proteins recognize each other across the membrane at distances of up to 10 nm 15 nm. As a result, attractive and repulsive long-range interactions across the membrane drive protein placement and organization before local electrostatic interactions between proteins form over short ranges of about 2 nm. Therefore, studying membrane-mediated interactions is important for understanding general membrane organization.

While circular dichroism, single-molecule fluorescence microscopy, Fluorescence Correlation Spectroscopy (FCS), and Förster Resonance Energy Transfer (FRET) have been employed to study membrane protein interactions and have provided invaluable observations that informed theory, these approaches are more indirect, make use of labels and/or are resolution limited. Here, we report an experimental design employing High-Speed Atomic Force Microscopy (HS-AFM) to directly visualize and quantify membrane-mediated interactions.

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We investigate the oligomerization and interaction energies of membrane proteins as a function of the bilayer thickness in which they are embedded using the water channel Aquaporin-Z (AqpZ) from Escherichia coli and synthetic lipids with defined hydrocarbon tail length as an experimental model system. The experimental system is well-defined: (i) AqpZ is solved to high-resolution by X-ray crystallography, providing details about the AqpZ structure and its hydrophobic thickness. (ii) An AqpZ-W14A mutant exposes surfaces to the membrane akin the AqpZ-WT tetramer, but has destabilized protomer interfaces, enabling us to study both the protein assembly and oligomerization processes. (iii) The thickness of the synthetic purified lipids used here have been resolved by small-angle X-ray diffraction, providing precise control and knowledge of the membrane environment in which the membrane-mediated protein interactions are measured. Finally (iv) HS-AFM films provide unique, direct structural and dynamic data useful for quantitative analysis.