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Lipid perturbation by membrane proteins and the lipophobic effect

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Abstract

Understanding how membrane proteins interact with their environment is fundamental to the understanding of their structure, function and interactions. We have performed coarse-grained molecular dynamics simulations on a series of membrane proteins in a membrane environment to examine the perturbations of the lipids by the presence of protein. We analyze these perturbations in terms of elastic membrane deformations and local lipid protein interactions. However these two factors are insufficient to describe the variety of effects that we observe and the changes caused by membranes proteins to the structure and dynamics of their lipid environment. Other factors that change the conformation available to lipid molecules are evident and are able to modify lipid structure far from the protein surface, and thus mediate long-range interactions between membrane proteins. We suggest that these multiple modifications to lipid behavior are responsible, at the molecular level, for the lipophobic effect we have proposed to account for our observations of membrane protein organization.

Keywords: molecular dynamics simulation; lipid structure; biological membranes; protein-lipid interactions

Introduction

Biological membranes are complex structures that form the barrier between the living cell and its environment. The protein and lipid components of the membrane organize themselves to form a dynamic 2D fluid, the structure and function of which is vital for life. Within this membrane, lipids, through their influence on the proteins, are important in membrane protein insertion [1–4], folding [4, 5], assembly into larger complexes [6, 7] and activity [8–10]. It is thus important to understand the complexity of lipid-protein interactions to decipher the interplay between protein sequences in one hand and the lipid composition on the other hand.

Current understanding of interactions between membrane proteins and their lipid environment comes from two different schools. First a mechanical elastic vision pioneered by Helfrich [11] considers the lipid membrane as an elastic sheet that is more or less deformed by curvature. This planar two dimensional vision was extended by the membrane mattress model [12] where the sheet was given thickness and embedded proteins. In this field view, the membrane perturbations are described in terms of hydrophobic mismatch [12–16] or curvature mismatch [17–22]. In both cases these are envisioned as a mismatch between the local lipid properties and those of the embedded proteins.

A second view relies on a chemical and molecular description where interactions and perturbations are seen as the affinity or binding of specific lipids or lipid classes to the membrane protein surface [23–25], and additionally the existence of annular lipids [26–28] with modified structure and dynamics. In this descriptions protein–protein interactions are influenced by modifications to both lipid packing and the annular lipid preferences [29]. This situation is similar to the solvation water found around soluble proteins which has modified structure and dynamics. The differences between the water and water far from solutes are responsible for the hydrophobic effect. Some of these changes in molecular properties of the solvent can be observed by experimental measures, such as the measurement of the NMR order parameter S_{CD}[30].

These two visions can both accommodate the possibility that the membrane contains regions with different chemical composition and mechanical properties, notably the existence of more or less stable domains or phase separated regions [20].

Despite its success in describing forces that arise from perturbation of the pure lipid membrane properties, the elastic description concerns a very abstract protein described essentially as a hydrophobic conical segment that gives little place to local interactions. In particular it can not represent the effect of the topography of protein surfaces.

The molecular view is increasingly extended, especially by integrating aspects that initially came from elastic models. However the description of the molecular perturbations at the origin of long range interactions is complex. An important question not currently be treated is how the modulation of membrane protein properties could influence long range interaction for example for the control of

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