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Review

The electrical interplay between proteins and lipids in membranes ☆

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ABSTRACT

All molecular interactions that are relevant to cellular and molecular structures are electrical in nature but manifest in a rich variety of forms that each has its own range and influences on the net effect of how molecular species interact. This article outlines how electrical interactions between the protein and lipid membrane components underlie many of the activities of membrane function. Particular emphasis is placed on spatially localised behaviour in membranes involving modulation of protein activity and microdomain structure.

The interactions between membrane lipids and membrane proteins together with their role within cell biology represent an enormous body of work. Broad conclusions are not easy given the complexities of the various systems and even consensus with model membrane systems containing two or three lipid types is difficult. By defining two types of broad lipid–protein interaction, respectively Type I as specific and Type II as more non-specific and focussing on the electrical interactions mostly in the extra-membrane regions it is possible to assemble broad rules or a consensus of the dominant features of the interplay between these two fundamentally important classes of membrane component. This article is part of a special issue entitled: Lipid–protein interactions.

Contents

1. Introduction

The interactions between lipids and proteins have been a subject of intense study for many years (see e.g. [42]), actually for rather longer than the fluid-mosaic membrane model has been in existence. Within membranes, the nature of these interactions fall into two broad categories and it's worth defining them separately to aid the discussion. Thus we

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deem Type I interactions to involve an explicit interaction between the protein and a particular membrane lipid that may be described as a specific molecular recognition event(s) as illustrated in Fig. 1A. In many cases this would involve the lipid(s) bound relatively tightly in a 'docking' site on the protein probably within one leaflet of the membrane bilayer. The second mode of interaction defined as Type II, is probably best described as a mean-field effect in which the lipid environment has an influence on the behaviour of the membrane protein as shown in Fig. 1B. The effect of the environment however may take several different forms such as mechanical (e.g. line tension, curvature etc., see [72]) or electrical effects such as static charges or dipole fields exerting distinct effects on the protein behaviour (e.g. [55]). These definitions of course, are closely allied to the much-debated, historical descriptions of annular and non-annular lipid protein assemblies (see [42]). For the sake of clarity we prefer to use the 'Types I & II' nomenclature as there are subtle and not so subtle differences between our working definition and the *annulus* hypothesis. In particular the Type II nomenclature accommodates the interactions of lipid with proteins and with each other in the extra-membrane regions via the supporting electrolyte media as illustrated in Fig. 2. We emphasise this region particularly as a significant element of membrane behaviour.

A spectrum of particular interactions is likely to exist between each of these possibilities with both types of interaction co-existing in some protein-membrane systems. Similarly, proteins may have reciprocal effects on the lipids and their behavioural characteristics (such as phase behaviour). Rather than solely take a retrospective or historical view however we hope to use this present forum to identify some of the key questions (and new ways to address them) as well as trying to rationalize the hitherto disparate views of membrane function in a cellular context.

2. Lipid–protein interactions and Membrane protein function

It will be necessary to discuss some aspects of Type I interactions further but it is the Type II category of molecular interaction that the present paper will mostly address. Nevertheless this still represents a huge body of work and even concentrating solely on the electrical interactions as the article's title indicates, necessitates consideration of a very large set of activities. This is particularly the case as it has

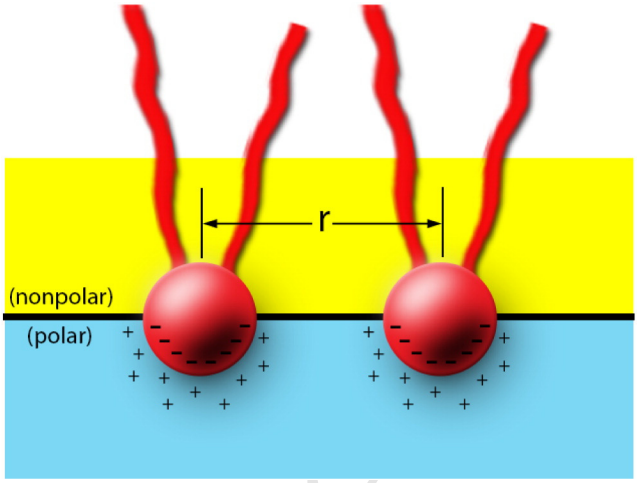

Fig. 2. Schematic of the intermolecular interactions between lipid headgroups in the aqueous (polar) and intra-membrane (non-polar) regions.

now become apparent that local (microdomain or membrane raft) structures have a bearing on membrane function (see e.g. [24]).

Although all molecular interactions relevant to cellular and molecular structures are electrical in nature they manifest in a rich variety of forms with their own characteristic range and influences on the net effect of how molecular species interact with each other see e.g. Fig. 3A. Collectively the distance-dependence of the attractive and repulsive interactions are embodied in the so-called DLVO theory (e.g. [35]) which has evolved to be a coarse grain or 'rule of thumb' methodology for predicting and describing the net interaction between macromolecular assemblies (e.g. colloids) as indicated in the idealised sketch in Fig. 3B. It's also worth noting that although the form of the DLVO energy-distance profile is reminiscent of the more explicit Leonard–Jones 6–12 potential profile, the formal rigour and molecular scales each formalism addresses are very different. The DLVO formalism is helpful for practical purposes as it simplifies the manifold ranges and magnitudes of the influences of 'each' of the forces outlined in Fig. 1 for macromolecular assemblies.

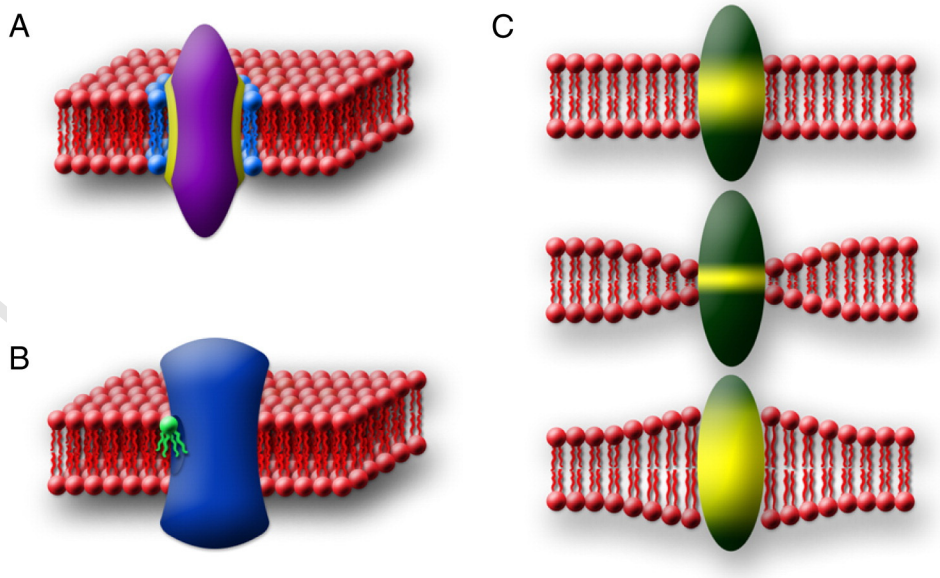

Fig. 1. Schematics of various types of lipid–protein interactions within membranes. A: Type I lipid–protein interaction i.e. illustration of a specific lipid binding or docking site on the body of the protein. B: Type II lipid–protein interaction i.e. illustration of a non-specific lipid mean-field effect of the lipid environment on a membrane protein. C: Lipid–protein mismatches in the membrane bilayer thickness with the hydrophobic regions of the membrane protein shown as the bright shaded regions (for more details see [42]).

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