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The interactions of peripheral membrane proteins with biological membranes

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ABSTRACT

The interactions of peripheral proteins with membrane surfaces are critical to many biological processes, including signaling, recognition, membrane trafficking, cell division and cell structure. On a molecular level, peripheral membrane proteins can modulate lipid composition, membrane dynamics and protein–protein interactions. Biochemical and biophysical studies have shown that these interactions are in fact highly complex, dominated by several different types of interactions, and have an interdependent effect on both the protein and membrane. Here we examine three major mechanisms underlying the interactions between peripheral membrane proteins and membranes: electrostatic interactions, hydrophobic interactions, and fatty acid modification of proteins. While experimental approaches continue to provide critical insights into specific interaction mechanisms, emerging bioinformatics resources and tools contribute to a systems-level picture of protein–lipid interactions. Through these recent advances, we begin to understand the pivotal role of protein-lipid interactions underlying complex biological functions at membrane interfaces.

1. Introduction

The classic fluid mosaic model of the plasma membrane (Singer and Nicolson, 1972) implies a homogenous distribution of lipids in the plane of the membrane bilayer. Within the framework of this model, proteins interacting with the membrane have frequently been viewed as islands floating in a sea of lipids. However, since the 1990s, the complementary hypotheses of lipid domain formation and protein-mediated control of lipid packing has triggered significant interest in studying the lateral organization of biological membranes. Since that time, it has also become widely recognized that proteins play important roles in the organization of plasma membranes. Protein–lipid interactions modulate lipid composition, membrane dynamics and structure (Kozlov, 2010; Phillips et al., 2009), which are fundamentally important for numerous cellular processes ranging from cytoskeleton assembly (Cabeen and Jacobs-Wagner, 2005) and membrane trafficking to intracellular and intercellular signaling (Martin, 1998). The supramolecular assemblies emerging from these protein–lipid interactions carry out an array of specialized cellular functions. Thus, beyond the characterization of individual molecular species, understanding of the highly dynamic, yet tightly controlled, interplay between membrane-associated proteins and membrane lipids is needed to describe many higher order cellular functions.

The composition of biological membranes is complex and varies with the type of cell or cellular compartment. Changes in lipid composition can result in the formation of microdomains with distinct physical properties, which arise from the interplay between the characteristic lipid headgroups and the hydrocarbon chains (Cevc, 1993). A membrane bilayer is a dynamic environment with varying dielectric properties ranging from nonpolar within the hydrocarbon chain core to polar at the headgroup-solution interface. In addition, the interfacial headgroup region can assume significant negative charge densities, which has important implications for recognition and recruiting membrane-associated proteins. Peripheral membrane proteins are recruited to and interact with cellular membranes through a series of distinct mechanisms. Specific membrane-targeting domains associate with a membrane through three major types interactions: electrostatic, hydrophobic and selective fatty acid modification. Thus, the targeted and occasionally transient interaction of a polypeptide with a bilayer is governed by a complex energy landscape.

The purpose of the present review is to summarize and exemplify mechanisms that drive the interactions between peripheral membrane proteins and membrane bilayers using specific examples from the literature. Furthermore, we highlight common experimental approaches to probe these interactions and

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bioinformatics as an emerging tool for predicting protein–membrane interactions.

We describe how charge complementarity between membrane and protein surfaces give rise to long-range electrostatic interactions, how proteins become tethered to membranes by inserting hydrophobic moieties into the hydrophobic hydrocarbon regions, and how some proteins use molecular recognition to selectively target specific membrane regions or other membrane proteins. Model membranes are widely used to probe protein–membrane interactions and are thus the system of choice for biophysical studies. However, recent advances in experimental techniques, such as fluorescence microscopy, super-resolution microscopy and neutron scattering, have enabled studies of protein–membrane interactions within the context of whole or live cells.

Computational biology, computational resources, and a rapidly growing number of sequenced genomes and metagenomes allow us to analyze vast amounts of sequence data by identifying relevant sequence features, such as amphipathic helices or motifs for post-translational lipid modifications. Advances in computational chemistry have enabled unprecedented insights into the interplay between peripheral membrane proteins and membranes. Although these interactions are highly complex and dynamic, there is much to be gleaned from understanding the underlying interaction mechanisms as they will help elucidate a range of cell-mediated processes, such as signaling, membrane trafficking, and cytoskeleton dynamics, but also provide insights relevant to antibiotic functionality, drug development and possible disease mechanisms.

1.1. Lipids, bilayers and proteins

Amphipathic lipids in aqueous solutions are entropically driven to self-assemble into bilayers, which enables compartmentalization and segregation of biochemical processes in cells. A lipid bilayer can be divided into a hydrophobic hydrocarbon core region and an interfacial, hydrophilic headgroup region. Bilayers are heterogeneous in terms of fatty acid core and headgroup composition. The membrane's interfacial region spans a distance of up to 15 Å from the hydrophobic core to the bulk aqueous solution (White et al., 2001). The most abundant lipid species found in biological membranes are glycerophospholipids, such as phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylserine (PS), phosphatidylglycerol (PG), phosphatidylinositol (PI) and phosphatidic acid (PA) (Fig. 1). Mammalian membranes also contain sphingomyelin (SM), the most common sphingolipid, and cholesterol, an amphiphilic sterol that resides between phospholipid molecules and has a hand in modulating membrane fluidity at varying concentrations depending on the tissue (Ramstedt and Slotte, 2002). SM was found to co-localize with cholesterol in plasma membranes and has been implicated in the formation of nanodomains (Mcintosh et al., 1992; Pathak and London, 2011; Smith et al., 2003).

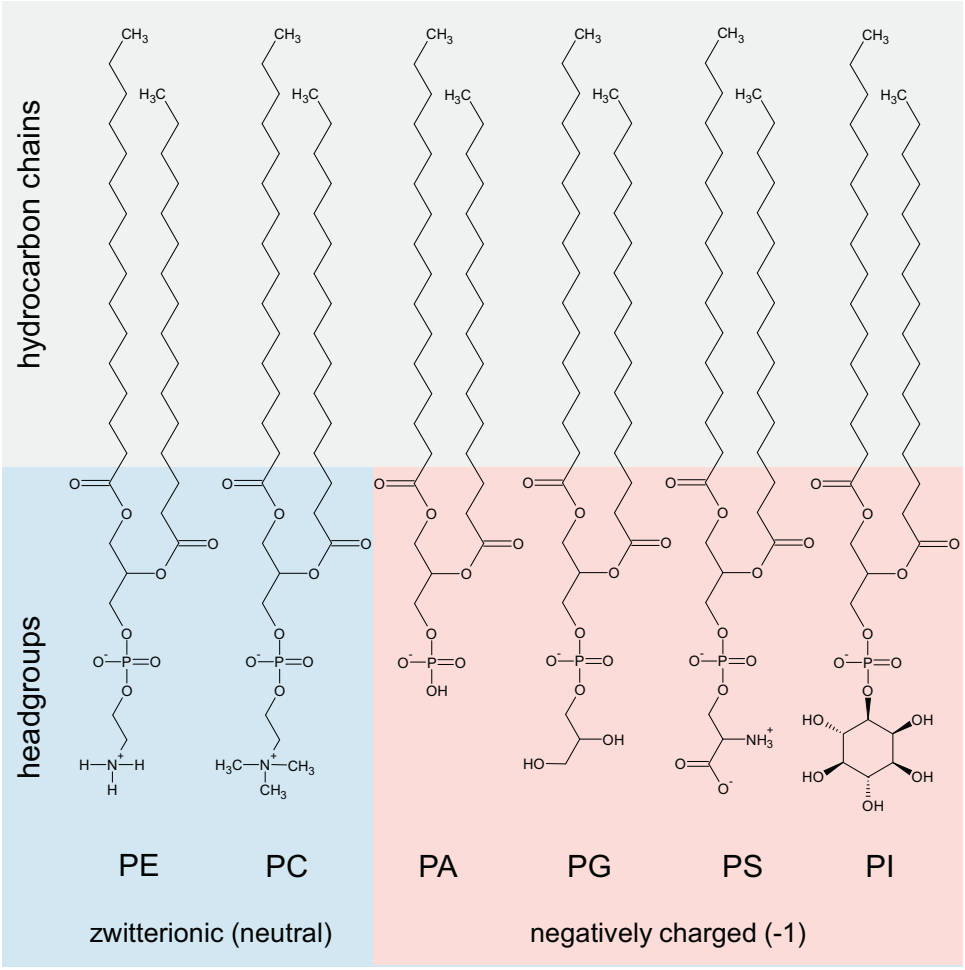

Fig. 1. Properties of common glycerophospholipid classes and headgroup charge characteristics. Phosphatidylcholine (PC) and phosphatidylethanolamine (PE) are both zwitterionic phospholipids and with zero net charge. Phosphatidic acid (PA), phosphatidylglycerols (PG), phosphatidylserine (PS) and phosphatidylinositol (PI), a glycolipid, are negatively charged phospholipids with a net charge of −1. Aliphatic palmitoyl chains represent the nonpolar hydrocarbon core.