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Review

Non-covalent binding of membrane lipids to membrane proteins ☆

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ABSTRACT

Polar lipids and membrane proteins are major components of biological membranes, both cell membranes and membranes of enveloped viruses. How these two classes of membrane components interact with each other to influence the function of biological membranes is a fundamental question that has attracted intense interest since the origins of the field of membrane studies. One of the most powerful ideas that driven the field is the likelihood that lipids bind to membrane proteins at specific sites, modulating protein structure and function. However only relatively recently has high resolution structure determination of membrane proteins progressed to the point of providing atomic level structure of lipid binding sites on membrane proteins. Analysis of X-ray diffraction, electron crystallography and NMR data over 100 specific lipid binding sites on membrane proteins. These data demonstrate tight lipid binding of both phospholipids and cholesterol to membrane proteins. Membrane lipids bind to membrane proteins by their headgroups, or by their acyl chains, or binding is mediated by the entire lipid molecule. When headgroups bind, binding is stabilized by polar interactions between lipid headgroups and the protein. When acyl chains bind, van der Waals effects dominate as the acyl chains adopt conformations that complement particular sites on the rough protein surface. No generally applicable motifs for binding have yet emerged. Previously published biochemical and biophysical data link this binding with function. This Article is Part of a Special Issue Entitled: Membrane Structure and Function: Relevance in the Cell's Physiology, Pathology and Therapy.

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1. Introduction

The membranes of cells (and enveloped viruses) are built largely from membrane proteins and lipids. What effects each membrane component may have on the other, and how they interact to modulate function in, on, and around biological membranes, have tantalized researchers for several decades. It is now possible to synthesize new data from three dimensional structures of membrane proteins with prior data from biophysical experiments to begin to answer the long-standing questions of the nature and extent of lipid–protein interactions in biological membranes, and what roles those interactions may play in biological membrane function.

In the most simple view, biological membranes can be considered to consist of two major classes of molecules: membrane lipids and membrane proteins. Three linked interactions must be considered in such a two component system: lipid–lipid interactions, protein–protein interactions, and lipid–protein interactions. These three sets of interactions are not independent. Perturbations in any one of these linked interactions can be expected to affect the other two. Protein–protein interactions are known from extensive studies with soluble proteins

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to play a central role in modulating and/or enabling function. Lipid–lipid interactions can affect the milieu in which the membrane proteins function (for example, a phase transition of the lipids to a gel state or the incorporation of high levels of cholesterol in the membrane, either of which will inactivate most transmembrane enzymes). Since in a biological membrane one may find dozens of unique membrane proteins and hundreds or thousands of unique membrane lipids, structure and function in the biological membrane are inherently more complex than just outlined. However, such a construct offers a useful structure with which to approach our subject. This review, therefore, will focus on lipid–protein interactions. Lipid–protein interactions, as just noted, can be affected by lipid–lipid interactions and protein–protein interactions. However because the former have been less intensively examined (due to lack of adequate experimental approaches), the focus will be on lipid–protein interactions while remaining cognizant of the other linked interactions.

Lipid–protein interactions will often influence membrane protein function. Lipids may force a protein conformational change to bury the hydrophobic surfaces of the membrane protein within the limited thickness of the hydrophobic interior of the membrane lipid bilayer. This can be particularly dramatic if a substantial hydrophobic mismatch occurs between the width of the hydrophobic surface of the transmembrane domain and the width of the bilayer. Transmembrane proteins express a hydrophobic surface on the transmembrane portion of the protein to coexist with, and match the dimensions of, the hydrophobic interior of the membrane bilayer. If the dimensions of the hydrophobic surface on the membrane protein are similar to the width of the hydrophobic interior of the bilayer, then these two components can find a ready accommodation. If however the protein is in a bilayer that is thinner than the hydrophobic surface on the protein, the protein may alter conformation (such as a tilt [1–3] or a bend [4,5] in the transmembrane portion) to better accommodate the hydrophobic portion of the bilayer, or the bilayer may distort to cover the hydrophobic surface on the transmembrane protein [6,7].

Lipids also can act as effectors that bind and alter membrane protein function. This role is analogous to effectors binding to soluble proteins in solution and inducing a change in protein function. Since the transmembrane proteins are in part within the lipid bilayer and the effective "concentration" of the lipids (solvent) in two dimensions within the bilayer is very high, any binding sites on the protein that can match the properties of one or more membrane lipids can be expected to be occupied by those lipids to some extent. The extent may be dependent upon protein conformation and therefore binding of these lipids can induce changes in membrane protein conformation and consequent changes in membrane protein function.

This latter set of possibilities has engendered considerable hypothesizing and experimenting. The opportunity for specific lipids to bind to particular membrane proteins and affect their function is a compelling concept. Such a concept would begin to provide an explanation for the observation of so many individual lipid species in most biological membranes. Until recently the paucity of atomic level structural information on membrane proteins considerably limited the ability of investigators to address this question directly. Prior to the availability of such detailed structural information, a number of (mostly) indirect experimental approaches were creatively applied that produced considerable support for a role of lipid binding to membrane proteins in regulation of membrane protein function (see for example, [8–12]). Recently considerable new information on atomic structure of transmembrane proteins has become available. Integrating those structural data with the previous biophysical data allows a much more extensive and satisfying exploration of the extent, nature and role of lipid–protein interactions in membranes.

Compared to a decade ago, there is now an abundance of structural data, in particular from X-ray crystallography, on lipid binding to membrane proteins. There are currently over 100 individual examples of a particular lipid binding to a particular membrane protein from X-ray crystal structures of transmembrane proteins (see Table 1). Below, the text will focus on individual classes of lipids, one at a time, that bind to membrane proteins and explore what is known for each of those lipids from X-ray crystallography data. Most earlier reviews on this

Table 1
Number of lipid binding sites in X-ray crystal structures of membrane proteins.

Lipid	PDB ID	Protein	# bound
Cholesterol	3AM6	H^+ pump rhodopsin ARII	2
	2YOO	Turkey β_1-adrenergic receptor	2
	2RH1, 3D4S	Human β_2-adrenergic receptor partial inverse agonist	2
	3PDS	Human β_2-adrenergic receptor agonist	1
	4EIY	Human A_{2A} (bRIL) adenosine receptor	3
	4DKL	Mouse μ-opiod receptor antagonist	2
	4IB4	Human 5-HT_{2B} ERG	1
	4HYT	Porcine Na^+K^+ATPase ouabain phosphorylated	1
	2ZXE	Shark Na^+K^+ATPase FXYD	1
	EMD-1079	Bovine rhodopsin	1
	2BG9	Torpedo nicotinic acetyl choline receptor (model into electron density)	1
DPG	2C3E, 1OKC	Bovine mitochondrial ADP/ATP carrier CATR	3
	1PPG	Bovine mitochondrial cytochrome bc_1, antimycin	1
	1KB9, 1P84	Yeast mitochondrial cytochrome bc_1, inhibitor	1
	2DYR, 1V54	Bovine heart cytochrome c oxidase	2
	4AYT	Human mitochondrial ABC transporter	2
	1NEK	*E. coli* succinate dehydrogenase	1
	1KQF	Formate dehydrogenase N	1
	1OGV, 1QOV	Photosynthetic rxn ctr *R. sphaeroides*	1
	4A2N	*Ma*-ICMT	1
	1M3X	*R. sphaeroides* photosynthetic rxn center	1
	1V54	*B. tau* cytochrome c oxidase	2
PG	1OCC	Bovine heart cytochrome c oxidase	3
	2DYR	Bovine heart cytochrome c oxidase	4
	2AXT	*T. elongatus* photosystem II	1
	1JBO	*S. elongatus* photosystem 1	3
	3LNM	Kv2.1–Kv1.2 chimera potassium channel	1
	2R9R	Kv2.1–Kv1.2 chimera potassium channel	>2
	4DOJ	BetP transporter	1
	4JBW	Maltose transporter	1
	1V54	*B. tau* cytochrome c oxidase	3
PE	1KB9	Yeast mitochondrial cytochrome bc_1, inhibitor	2
	1P84	Yeast mitochondrial cytochrome bc_1, inhibitor	3
	1BCC	Avian cytochrome bc_1	2
	1PPJ	Bovine cytochrome bc_1 inhibitor	2
	1M56	*R. sphaeroides* cytochrome c oxidase	6
	2DYR, 1OCC	Bovine cytochrome c oxidase	3.5
	1QOV	*R. sphaeroides* photosynthetic rxn center	1
	1ZOY, 2FBW	Porcine mitochondrial respiratory complex II	2
	1EYS	*T. tepidum* photosynthetic rxn center	1
	1XIO	Anabaena sensory rhodopsin	>4
	1GZM	Bovine rhodopsin	1
	3W5A	Rabbit Ca pump sarcoplasmic reticulum	3
	3ZUY	Bacterial Na^+ bile acid cotransporter	2
	2ZZ9	Aquaporin	5
	1V54	*B. tau* cytochrome c oxidase	3
	1NEK	*E. coli* cytochrome c oxidase	1
PI	1KB9	Yeast mitochondrial cytochrome bc_1, inhibitor	1
PIP_2	3SYA	Mammalian GIRK2 potassium channel	1
PC	2DYR	Bovine heart cytochrome c oxidase	1
	1P84	Yeast mitochondrial cytochrome bc_1, inhibitor	2
	1KB9	Yeast mitochondrial cytochrome bc_1, inhibitor	1
	1OKC	Bovine mitochondrial ADP/ATP carrier	2
	2Z73	Squid rhodopsin	1
	3AYN	Squid isorhodopsin	1
	3B8E	Porcine renal Na^+K^+ATPase	1
	4AW6	Zinc metalloprotease, ZMPSTE24	1
	3RVY	Voltage gated channel NavRh	1
	4EKW	Voltage gated channel NavRh	4
	2B6O	Aquaporin	Annulus
	2XTV	*E. coli* rhomboid protease GLPG	Annulus
	1QLE	*P. den.* cytochrome c oxidase	2
	1V54	*B. tau* cytochrome c oxidase	1