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Review

Complementary biophysical tools to investigate lipid specificity in the interaction between bioactive molecules and the plasma membrane: A review

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Plasma membranes are complex entities common to all living cells. The basic principle of their organization appears very simple, but they are actually of high complexity and represent very dynamic structures. The interactions between bioactive molecules and lipids are important for numerous processes, from drug bioavailability to viral fusion. The cell membrane is a carefully balanced environment and any change inflicted upon its structure by a bioactive molecule must be considered in conjunction with the overall effect that this may have on the function and integrity of the membrane. Conceptually, understanding the molecular mechanisms by which bioactive molecules interact with cell membranes is of fundamental importance.

Lipid specificity is a key factor for the detailed understanding of the penetration and/or activity of lipid-interacting molecules and of mechanisms of some diseases. Further investigation in that way should improve drug discovery and development of membrane-active molecules in many domains such as health, plant protection or microbiology.

In this review, we will present complementary biophysical approaches that can give information about lipid specificity at a molecular point of view. Examples of application will be given for different molecule types, from biomolecules to pharmacological drugs. A special emphasis is given to cyclic lipopeptides since they are interesting molecules in the scope of this review by combining a peptidic moiety and a lipidic tail and by exerting their activity via specific interactions with the plasma membrane.

Contents

Abbreviations: Aβ peptide, Beta Amyloid peptide; AD, Alzheimer Disease; AFM, Atomic Force Microscopy; AMP, Antimicrobial Peptide; ATR-FTIR, Attenuated Total Reflection Fourier Transform Infrared Spectroscopy; AZT, Azithromycin; BAM, Brewster Angle Microscopy; BM, Big Monolayer; BODIPY, Boron-dipyrromethene; C16BC, Hexadecylbetainate chloride; CG, Coarse Grained; CD, Circular Dichroism; Chol, Cholesterol; CLP, Cyclic lipopeptide; CMC, Critical Micelle Concentration; DHE, Dehydroergosterol; DIG, Detergent-Insoluble Glycolipid-(enriched complex); DHPC, 1,2-dihexanoyl-sn-glycero-3-phosphocholine; DMPA, 1,2-dimyristoyl-sn-glycero-3-phosphatidic acid; DMPC, 1,2-dimyristoyl-sn-glycero-3-phosphocholine; DMPE, 1,2-dimyristoyl-sn-glycero-3-phosphoethanolamine; DODAB, Dioctadecyldimethylammonium bromide; DOPC, 1,2-dioleoyl-sn-glycero-3-phosphocholine; DPPC, 1,2-dipalmitoyl-sn-glycero-3-phosphocholine; DPPE, 1,2-dipalmitoyl-sn-glycero-3-phosphoethanolamine; DPPG, 1,2-dipalmitoyl-sn-glycero-3-phosphoglycerol; DPPS, 1,2-dipalmitoyl-sn-glycero-3-phosphoserine; DRM, Detergent Resistant Membrane; FRET, Forster Resonance Energy Transfer; GIPC, Glycosphingolipid; GM1, Monosialotetrahexosylganglioside; GUV, Giant Unilamellar Vesicle; GS, Gramicidin S; HM, Hypermatrix; IR, Infrared Spectroscopy; IRRAS, Infrared Reflection Adsorption Spectroscopy; ITC, Isothermal Titration Calorimetry; LB, Langmuir–Blodgett; Ld, Liquid disordered; LGP, Lipophilic Glutathioine Peptide; Lo, Liquid ordered; LPS, Lipopolysaccharide; LUV, Large Unilamellar Vesicle; MD, Molecular Dynamics; MP, Membrane Protein; NBD-(DP)PE, N-7-nitro-2-1-3-benzoxadiazol-4-yl (dipalmitoyl)phosphatidylethanolamine; NMR, Nuclear Magnetic Resonance; NR, Neutron Reflectivity; PA, Phosphatidic acid; PC, Phosphatidylcholine; PDB, Protein Data Bank; PE, Phospatidylethanolamine; PG, Phosphatidylglycerol; Phi, Hydrophilic; Pho, Hydrophobic; PI, Phosphatydilinositol; PLA1, Phospholipase A1; PL, Phospholipid; PMF, Potential of Mean Force; PM-IRRAS, Polarization Modulation Infrared Reflection Adsorption Spectroscopy; PM, Plasma Membrane; POPC, 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine; POPE, 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphoethanolamine; POPG, 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphoglycerol; PS, Phosphatidylserine; QCM-D, Quartz Cristal Microbalance with Dissipation; R18, Octadecyl Rhodamine B chloride; RhBG, Rhamnose-Based Glycolipids; Rh-PE, Rhodamine-phosphatidylethanolamine; SF, Surfactin; SIMS, Secondary Ion Mass Spectrometry; SIV, Simian Immunodeficiency Virus; SLB, Supported Lipid Bilayer; SM, Sphingomyelin; SPR, Surface Plasmon Resonance; SUV, Small Unilamellar Vesicle; TOF-SIMS, Time-of-Flight Secondary Ion Mass Spectrometry; TR-DPPE, Texas-Red Dipalmitoylphosphatidylethanolamine

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1. Plasma membrane

1.1. General concept

As compared to nucleic acids, responsible for the genetic information and proteins, that perform most of the functional and enzymatic tasks, lipids often appear as “Cinderella” in the biomolecules family, being considered as just sitting there passively.

The basic principle of the organization of membranes looks very simple, formed by lipid bilayers where the polar headgroups are facing the aqueous environment and the hydrocarbon tails facing the interior of the bilayer, yet the details are surprisingly complex. Hence, plasma membranes (PMs) are complex dynamic entities which delimit the cell from its environment. They are the point of exchange with adjoining cells, and between the cell and the external medium. They are the primary place where signal recognition and transduction into intracellular responses for nutritional uptake, environmental responses, and developmental signalling occurs [1,2]. Over years, it has become increasingly clear that if they are laterally fluid, they also can adopt a fascinating range of spatial organizations like the formation of transient local ordered clusters which are biologically important for several functional states of membrane proteins [2].

The cell membrane is a carefully balanced environment and any change inflicted upon its structure by a bioactive molecule must be considered in conjunction with the overall effect that it may have on the function and integrity of the membrane [3]. Understanding the mechanism at the molecular level by which bioactive molecules interact with cell membranes is therefore of fundamental importance.

1.2. Plasma membrane composition

PMs are composed by three main classes of lipids: glycerolipids (mainly phospholipids—PL), sphingolipids and sterols [2,4]. However, between species or cell types within a species, the lipid composition of PM can show a high degree of diversity; Table 1 illustrates this complexity.

In eukaryotic cells, the major structural lipids are glycerophospholipids, such as phosphatidylcholine (PC), phospatidylethanolamine (PE), phosphatidylserine (PS) and phosphatidic acid (PA) [5–8]. Their hydrophobic tails, with chain length varying mostly from 14 to 22 carbons are either satured or *cis*-unsaturated. PC is the most abundant, accounting for more than 50% of PL [9]. The backbone of sphingolipids is constituted by a ceramide with saturated or *trans*-unsaturated hydrophobic chains. In mammalian cells, sphingomyelin (SM) and glycosphingolipids are the most abundant. Concerning sterols, cholesterol (Chol) is predominating in mammals and has a preferential interaction with sphingolipids, forming the so-called rafts domains (see below).

It is worth noting that the variation in headgroups and aliphatic chains permits the existence of more than a thousand different lipids.

Table 1
Lipid composition (in molar %) of different cell membranes in eukaryotic or prokaryotic organisms.

Lipids	Eukaryotic cells					Prokaryotic cells			
	Human erythrocyte	Human alveolar macrophage	Rat liver	*A. thaliana* leave	*S. cerevisiae*	*B. megaterium* Gram +	*S. aureus* Gram +	*P. aeruginosa* Gram −	*E. coli* Gram −
PC	16	30	25	17	25				
PE	15	21	12	18	10	73		60	82
PS	7	21	2	3	3				Traces
PG				4		27	58	21	6
CL					~2		42	11	12
PI	0.5		4	5	9				
PA	1				5				
SL[a]	14 (SM)	7 (SM)	13	7 (GIPC[a])	10–20 (MIPC)				
Sterol[a]	46 (chol)	8 (Chol)	43 (Chol)	46 (sitosterol)	30–40 (Ergosterol)				
Others	0.5	13	1						
Ref	[5,6]	[7]	[8]	[1,10,11]	[13,15,17]	[8]	[19]	[19]	[19]

PC: phosphatidylcholine, PE: phosphatidylethanolamine, PS: phosphatidylserine, PG: phosphatidylglycerol, CL: cardiolipin, PI: phosphatidylinositol, PA: Phosphatidic acid, SL: sphingolipid, SM: sphingomyelin, GIPC: glycosyl inositol phosphorylceramides, MIPC: mannosyl inositol phosphorylceramides.
[a] The most abundant lipid of these categories is indicated in brackets.

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