Advances in Colloid and Interface Science 205 (2014) 207–220

Contents lists available at ScienceDirect

Advances in Colloid and Interface Science

journal homepage: www.elsevier.com/locate/cis

Model cell membranes: Discerning lipid and protein contributions in shaping the cell

Thomas Günther Pomorski [a], Tommy Nylander [b], Marité Cárdenas [c,*]

[a] Centre for Membrane Pumps in Cells and Disease-PUMPKIN, Department of Plant and Environmental Sciences, University of Copenhagen, Thorvaldsensvej 40, DK-1871 Frederiksberg C, Denmark
[b] Department of Chemistry, Division of Physical Chemistry, Lund University, Gettingevägen 60, SE-22100 Lund, Sweden
[c] Department of Chemistry/Nano-Science Center, University of Copenhagen, DK-2100 Copenhagen, Denmark

ARTICLE INFO

Available online 7 November 2013

Keywords:
Cell membranes
Lipids
Proteins
Vesicles
Bilayers
Nanodiscs

ABSTRACT

The high complexity of biological membranes has motivated the development and application of a wide range of model membrane systems to study biochemical and biophysical aspects of membranes *in situ* under well defined conditions. The aim is to provide fundamental understanding of processes controlled by membrane structure, permeability and curvature as well as membrane proteins by using a wide range of biochemical, biophysical and microscopic techniques. This review gives an overview of some currently used model biomembrane systems. We will also discuss some key membrane protein properties that are relevant for protein–membrane interactions in terms of protein structure and how it is affected by membrane composition, phase behavior and curvature.

Contents

1. Introduction

Biological membranes serve as barriers, gatekeepers and they are an important matrix for cellular processes. The cell membrane, or plasma membrane, defines the external boundary of every cell separating the cytoplasm from the surrounding environment and strictly regulating in- and output of material and information. Eukaryotic cells contain in addition numerous subcellular membranes that divide the cytoplasm into multiple compartments (organelles), thereby allowing different functions to occur efficiently and simultaneously in different parts of the cell (Fig. 1). Cell membranes and cell organelles are formed by directed self-assembly of a complex mixture of lipids and proteins. The final structure of each organelle results from the exact molecular composition of their membranes, which is spatially and temporarily tightly regulated. A particular lipid composition is associated to certain type of cell organelles [1,2]. For example, the inner mitochondrial membrane is enriched in cardiolipin [3–5], a phospholipid with four acyl chains that

* Corresponding author. Tel.: +45 35 32 04 31; fax: +45 35 32 02 14.
E-mail address: cardenas@nano.ku.dk (M. Cárdenas).

0001-8686/$ – see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.cis.2013.10.028

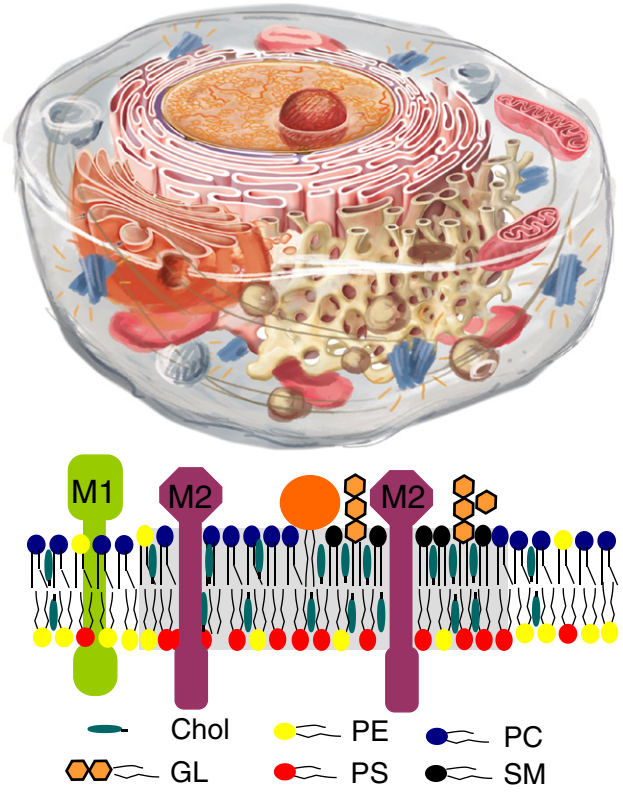

Fig. 1. A schematic diagram of a eukaryotic cell, emphasizing the rich diversity of shapes and structures present in the cell. Each cellular membrane contains unique sets of proteins and has a complex lipid composition, often including an asymmetric distribution of phospholipids between the opposing leaflets of the bilayer. In addition, cellular membranes display a lateral heterogeneous organization by the clustering of specific lipids into highly condensed domains. Various domains of different composition may occur within a monolayer and domains in both monolayers may colocalize (gray bilayer). A variety of membrane proteins can partition into lipid domains (gray bilayer, M2 in contrast to M1). PC, phosphatidylcholine; PE, phosphatidylethanolamine; PS, phosphatidylserine; SM, sphingomyelin, Chol, cholesterol; GL, glycolipid.

tends to form assemblies with large inverse curvature [6,7] and therefore favors membrane folding [8]. The importance of curvature and non-lamellar lipid based phases in many biological systems has recently been reviewed by the group of Yuru Deng [9–11].

In 1972, the "fluid mosaic" model for the biological membranes was introduced [12]. In this model, membrane proteins are embedded in the viscous but fluid lipid bilayer, and thus are able to freely diffuse within the lipid bilayer plane. The "fluid mosaic" model assumes that no specific interactions between lipids and proteins occur, and thus these biomolecules should behave rather independently. However, there is now compelling evidence that cellular membranes are more complex with preferential lipid–lipid and lipid–protein associations. The composition of the lipid membrane determines the fluidity, curvature as well as the phase separation in terms of in plane domain formation of the bilayer. Indeed, a delicate balance of lipids that promote different curvatures (see lipid packing, Section 2.1) is determinant for the healthy function of *Escherichia coli* (*E. coli*) bacterium [13,14]. Moreover, micro-scale heterogeneity of cellular membranes due to the phase separation of lipids (see lipid demixing, Section 2.2) has consequences for the recruitment and concentration of proteins, regulation of protein–protein interactions with the membrane, and cell signaling functions. The more recent "flexible surface" model for the cell membrane [15,16] takes into account that lipid–lipid and protein–lipid interactions affect the membrane properties.

In this regard, proteins and protein complexes embedded in the membrane as well as those present in the dense cytoplasm [17–19] that interact with cellular membranes, can affect the membrane curvature [20,21]. It has been shown that many chemical reactions of the cell take place in complexly shaped organelles where the membranes are highly curved [22]. Besides creating a large specific area, tubular and curved structures like cubic liquid crystalline phases provide tortuous channels that can control transport of cellular material. Moreover, the high viscosity of the cytoplasm [17,19] (as compared to water) provides an additional mechanism for regulating protein–protein and protein–membrane interactions due to crowding and this has received little attention so far. Many biomolecular interactions under physiological conditions are characterized by weak forces of transient character, and therefore higher encounter probability is desired for these interactions to have an impact [19,23]. The consequences of protein–lipid interactions for the cell membrane can be large and lead to major local changes in the composition of the membrane that trigger cell membrane invagination and vesiculation (for a review see, *e.g.* Ref [24] and Ref [25]).

Before describing some general characteristic of cellular membranes, we would like to give two specific examples that illustrate the importance of both the lipid and protein contribution to the curvature of cellular membranes and *vice-versa*. The first example is that of the endoplasmatic reticulum (ER), which is one of the most intricate organelles in eukaryotic cells. The ER membrane has a branched structure that is bicontinuous, *i.e.* continuous both in the lipophilic and hydrophilic phases (Fig. 2A). Certain lipid mixtures can form self-assembled structures of high curvature, like for instance the monooleindioleoylphosphatidylcholine (DOPC)-water mixture [26–28] that forms a bicontinuous cubic phase with a diameter of the lipid aqueous tubula in the order of 10 nm (Fig. 2B). However, the ER displays tubular structures with diameters ranging from 30 to 100 nm [29]. Thus, lipids alone can form similar intriguing structures, but cannot alone account for the dimensions of the intricate membrane structure of the ER and a protein contribution is required as recently demonstrated [11,30–32].

The second example is that of rod shaped bacterial cells such as *E. coli* cells. The plasma membrane of this bacterium has the shape of prolated spheroid with the long axis being about 1 μm (Fig. 3A). Renner and Weibel showed recently [33] that the high cell-wall curvature at the poles of the *E. coli* bacterium is enriched with cardiolipin, a lipid that promotes the formation of reversed self-assemblies (see lipid packing, Section 2.1). In mixtures, the presence of lipids that promote different curvatures often lead to the formation of microdomains of distinct composition and probably of different fluidity (Fig. 3B). Moreover, certain membrane proteins may specifically associate within these cardiolipin-rich domains and further increase the membrane curvature [34]. Thus, geometrical and physical constraints of the cell can determine the spatial organization of proteins and lipids in cellular membrane.

It is clear that the study of cellular membrane structure and function under physiological conditions is challenged by their enormous complexity. Therefore, the reconstitution of cellular or molecular subsystems of reduced complexity in cell-free, well-defined environments has been, and remains, an important approach in membrane biology. This review summarizes currently used model membrane systems. We will also discuss some key membrane protein properties relevant for protein–membrane interactions and the consequences for membrane curvature.

2. Characteristics of cellular membranes

2.1. Lipid packing

Our understanding of polar lipids self-assembly and their rich lyotropic phase behavior with 1D, 2D and 3D periodic liquid crystalline structures derives from the pioneering works of Luzzati and colleagues in France [35] and Fontell, Larsson and colleagues in Sweden [36–38] from the late 1960's. It was early established that many phospholipids including phosphatidylcholines spontaneously formed lipid bilayers in aqueous dispersions under pH and ionic strength similar to that of biological systems. However, a variety of lipids such as cardiolipin [6],