Biological membranes: structure and function

\n[toc title="Table of Contents"]\n

\n \t

1. Phospholipids \n \t
2. Lipid composition of biomembranes \n \t
3. Lipid polymorphism \n

\n[/toc]\n \n

The biological membranes, or biomembranes, are thin layers vital to organize biochemical processes that require compartmentalization. In all living cells, biological membranes carry out the function of « barrier» that not only divide the cell from the environment, but also the internal cell volume into comparably isolated « compartments» such as nuclei, mitochondria, chloroplasts, endoplasmic reticulum and the Golgi apparatus [1].

Biological membranes are built of a double layer of phospholipid molecules (which is often called « bilayer») and are practically impermeable for ions and polar water-soluble molecules. This lipid bilayer includes numerous intrinsic protein molecules and molecular complexes, involved in transport processes across membranes, like pumps and channels for ions and molecules. Their functions include the active transport of protons by the light driven rhodopsin, of sodium and potassium by the ATP-consuming Na+/K+-ATPase, and passive transport by ion channel proteins, e. g., Na+-channel and K+-channel. This selective permeability causes an irregular distribution of ions between the intracellular and extracellular milieu, which lies in the

basis of the processes of intracellular regulation and signal transfer in the form of electrical impulse between cells.

The typical thickness of a lipid bilayer is about 5nm. Thus, these are extremely thin layers as compared to the typical dimensions of cells (several 10 µm). Such membranes are flexible, heterogeneous and permeable. However, these properties depend on the conditions, for example on temperature, pressure, electrical field, pH, salt concentration, but also the presence of proteins and protein conformation. This basically means that the state of a biological membrane depends on all thermodynamic variables.

Our understanding of the structure and properties of biomembranes has increased steadily since 1895 when Ernest Overton first described the cell membrane as a covering structure made up of lipid molecules. Years later, in 1925, Gorter and Grendel concluded that the erythrocyte membranes were formed by two lipid layers [2] and, in 1972, Singer and Nicolson’s fluid mosaic model represented a qualitative leap in our understanding of the membrane structure and functionality [3]. Nowadays, the lipid membrane is no longer defined as just a passive film that blocks the passage of water and solutes, and in which the ‘ truly’ regulatory elements (proteins) are inserted. The development of novel biophysical techniques has made it possible to attribute new properties to membranes not previously defined in Singer and Nicolson’s model [4, 5].

The complex dynamics of the plasma membrane goes far beyond the basic functions, since it also participates in lipid-lipid and lipid-proteins interactions. These interactions modify the lipid bilayer itself, influencing

protein activity. In turn, the presence of proteins also effects the structure of membranes.

The protein density seems to be higher than was originally thought, and lipids and proteins are clearly not homogeneously distributed since lipid-lipid, lipid-protein and protein-protein interactions induce the formation of domains of specific lipid and protein compositions.

In addition, interactions between different molecules and cytoskeletal proteins in these domains also play an important role in defining membrane microdomains. Moreover, Singer-Nicolson’s model did not contemplate the existence of transmembrane proteins with a hydrophobic region thicker than that of the phospholipid bilayer. The currently accepted model postulates that proteins are not the elements that adapt to the thickness of the membrane but rather, lipids have certain flexibility to accommodate proteins with different sized hydrophobic transmembrane regions. Thus, the bilayer thickness may vary over the entire surface of the membrane.

Phospholipids

Phospholipids are an important class of biomolecules and they are the fundamental building blocks of cellular membranes. The structure of the most common class of phospholipids consists of two fatty acyl chains, each typically having an even number of carbon atoms between 14 and 20, esterified at the sn-1 and sn-2 positions of glycerol, and contain a polar or charged head group linked by a phosphate residue at the sn-3 position.

Phospholipid structures

The head group forms a hydrophilic region and determines the type of phospholipid. The fatty acyl side chains are hydrophobic; this amphipathic property of phospholipids provides the basis for the compartmentalization of cells.

Common phospholipids, widely distributed in nature, are produced by further reaction of the phosphate group in phosphatidate with an alcohol, such as serine (PS), phosphatidyl inositol (PI), and phosphatidyl glycerol (PG); or dipolar (having separate positively and negatively charged regions), for example, phosphatidyl choline (PC), and phosphatidyl ethanolamine (PE). A typical phospholipid arrangement is the presence of a saturated fatty acid, such as palmityc or stearic acid, at the sn-1 position, and an unsaturated or polyunsaturated fatty acid, such as oleic (18: 1) or arachidonic (20: 6) acid, at sn-2 position.

Another class of phospholipids is the sphingolipids. A sphingolipid molecule has the phosphatidyl-based headgroup structure but, in contrast to a common phospholipid molecule, contains a single fatty acid and a long-chain alcohol as its hydrophobic components. Additionally, the backbone of the sphingolipid is sphingosine, an amino alcohol (rather than glycerol). The structure of a representative sphingolipid, sphingomyelin (SM), is also shown in Table 1 (prenderla dalla tesi).

The size, shape, charge, and chemical composition of different phospholipid classes play a role in the formation and maintenance of the plasma membrane of cells, as well as membranes surrounding subcellular organelles and vesicles. An asymmetric distribution of phospholipid types within the

membrane imparts different functional characteristics between the inner and outer leaflets.

Phospholipids are essential for the absorption, transport and storage of lipids. They are involved in stabilizing proteins within the membrane, facilitating the active conformational structure of proteins, and as cofactors in enzymatic reactions.

Lipid composition of biomembranes

When talking about the composition of biological membranes, one has to distinguish proteins that are encoded in the genome and the lipid composition that is not encoded in the genome. The latter rather adapts to the environmental conditions, partially by the control of membrane active proteins that display an activity depending on the physical state of the membrane.

The composition of membranes is complex. There are hundreds or evens thousands of different lipid species and further thousands of different membrane proteins. The composition of membranes is different not only between different species, but also between different cell types of the same organism, and even between the membranes of different organelles within the same cell [1].

Proteins act, e. g., as catalysts and the importance of their role seems intuitively clear, while the role of the lipid membrane and the range of different lipid compositions are less obvious and there is no agreement in the biophysical community yet on what the purpose of the heterogeneity of the lipids precisely is. Moreover, the lipid composition of the inner and the outer

leaflet of some membranes may also be asymmetric. For example, while phospholipids are distributed equally in both monolayers of the endoplasmic reticulum, where most lipids are synthesized, the lipid distribution of the major membrane lipids in the inner and outer leaflets of the erythrocyte membrane is completely different and is presented in Fig. 3. The choline-containing phospholipids, SM and PC, are localized predominantly in the outer monolayer of the plasma membrane. The aminophospholipids PS and PE, by contrast, are enriched in the cytoplasmic leaflet of the membrane due to the action of various enzymes [6-10].

Besides this cross-sectional asymmetry, many membranes also show an important lateral asymmetry.

Microdomains called « lipid rafts », primarily occurring in nervous tissue, coexist in a single membrane and maintain their own special biophysical properties by restricting or impairing the intermixing of their lipid and protein components [11].

Such domains have recently become a focus of increasing interest due to their implication in many cellular processes such as signal transduction, vesicular trafficking and viral infection. Over a decade ago, the lipid raft was first defined as a detergent-resistant transient microdomain composed of cholesterol (CHOL), SM, glycosphingolipids and different proteins that attach to the lipid structure via a glycosylphosphoinositol (GPI) anchor, a fatty acid modification or a hydrophobic amino acid sequence [12]. The carbonyl group of sphingolipids forms a hydrogen bond with the 3β-OH of CHOL, forming a rigid structure with the phospholipid acyl chains fully extended, but with

certain rotational and bending mobility. Cholesterol appears to be a key player in the formation of lipid rafts. It is planar and inflexible and would pack better with saturated fatty acid chains and could also induced them to elongate to form lower energy zig-zag structures in which all the methylene groups are anti. This liquid-ordered (Lo) structure is more fluid than the gel lamellar phase (Lβ), although it is more rigid than the liquid crystalline phase (Lα). By contrast, a liquid-disordered phase (Ld) contains a small amount of cholesterol with unsaturated PCs, producing a less compact structure that resembles the Lα structure. In Ld regions, the surface packing is looser than in Lo regions; it is especially loose in regions with high PE content, where proteins with bulky membrane anchors (e. g. isoprenyl moieties) can find an appropriate docking space for their membrane binding.

Lipid polymorphism

When dispersed in aqueous solutions, lipids can organize in different ways depending on their molecular structure, water concentration, pH, ionic strength or system pressure [13, 14]. Such polymorphism among lipids is important in cell processes such as membrane fusion and fission, vesicular trafficking, macromolecule transport through the membrane and the stabilization of protein complexes in the lipid bilayer [15, 16]. Moreover, the way in which lipids are organized affects their interactions with membrane proteins, thereby modulating their activity [17, 18].

A lipid phase is a thermodynamic concept that defines each of the different structural stages of matter, like water in the solid or liquid state. A lipid phase refers to a specific conformation adopted by lipids in an aqueous solution (i. e. how lipids organize into supramolecular structures). Lipid

phases may be classified according to three criteria: (i) the type network; (ii) the packing of the acyl chains; and (iii) the curvature of the whole structure.

The most widely used nomenclature for their designation involves the use of a letter and a subscript, as proposed by Luzzati [19]. The type of network may be: unidimensional, as a lamellar (L) or micellar structures; bidimensional, like in hexagonal (H) phases, or cubic (Q) and crystalline three-dimensional (C) structures. The subscript indicates the degree of acyl chain packing: « α » refers to disordered hydrocarbon chains (fluid); « β », ordered (gel); « β'», rippled-ordered; and « c », crystalline. In addition, the lipid structure may adopt a positive curvature with the phospholipid acyl chains facing inward (type I), or a negative curvature where the acyl chains are outwards (type II or inverted). The most relevant lipid structures from a biological point of view are the lamellar, micellar, inverted hexagonal (HII) and inverted cubic (QII) phases (figure 6). Lamellar phases include Lβ, Lα Lo and Ld.

The coexistence of large amounts of CHOL (over 20 mol%), SM and glycerophospholipids (e. g. PC) leads to the formation of Lo structures, like lipid rafts, where CHOL and SM molecules are tightly packed.

The macroscopic lipid organization within a membrane in part depends on the monomeric structure of its lipids [21] (figure 7). Lipids with a cylindrical shape, like SM and PC, form lamellar structures with a global curvature of zero. Other lipids, such as PE, CHOL or diacylglycerol, form membranes with negative curvature strain due to their truncated cone shape. These molecules induce the formation of inverted hexagonal phases in vitro.

Finally, molecules whose hydrophilic region occupies a larger area than the hydrophobic moiety (e. g. detergents and lysophospholipids) possess an inverted cone shape and they induce a positive curvature in the lipid structure.

Figure: In the left-hand column of this figure is schematically represented three alternative bilayer motifs. Representations of the ‘ shapes’ of the lipids packed in a bilayer have been exaggerated in order to emphasize the consequences of packing into a flat structure phospholipids that have an effectively small headgroup (negative curvature strain), a headgroup of size comparable to the cross-section of the acyl chains (stable bilayer) or a phospholipid with a large headgroup (positive curvature strain). The right-hand panels indicate the types of curved structures that the corresponding types of lipids can form. Wavy lines indicate the location of the water [17].

On the whole, biological membranes adopt a lamellar structure, though certain transient regions with a high concentration of specific lipids may exist that induce a local curvature other than zero. This modulation in membrane lipid composition is essential to many cell processes including membrane fusion-fusion [22], the formation of proteolipidic pores [23] or the binding of membrane proteins to the lipid bilayer [18, 24].