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Membranes for Life and Life for Membranes

1.1 CELL MEMBRANES: THE ROLE OF FATTY ACIDS AND THE EXCLUSION OF TRANS ISOMERS

The cell membrane represents the fundamental structure and organizational element in the cells of living organisms. In fact, no cell can exist without the membrane; actually, cell reproduction and multiplication, such as in cancerogenesis, implies formation of membranes [1]. The complex mixture of lipids in an overall fluid state, where proteins and other molecules such as cholesterol are immersed, identifies the cell space and its boundary with the extracellular environment, but its behavior is not like that of a wall. Instead, this is the structure through which all communications and exchanges useful to cell life occur, and in the twenty-first century it represents the most direct and innovative site for correlation with the health condition.

The fundamental unit of the membrane assembly is the phospholipid molecule, with a characteristic structure that is defined as amphipatic. This means that in the same molecule two different parts coexist: the hydrophilic and the hydrophobic parts. The hydrophobic part cannot stay in contact with water, the biological solvent, since it is impossible to establish any type of interaction (the so-called hydrogen bonding). Therefore, the hydrophobic effect occurs, which leads to the perfect separation of the water molecules and the hydrophobic components in two phases, as is observed between oil and water. In phospholipids the hydrophilic part

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is called the "head" and the hydrophobic part is called the "tail"; as the structure shown in Figure 1.1 indicates, the hydrophobic part is made of long fatty acid chains (generally with hydrocarbon chains containing from 12 up to 26 carbon atoms), with and without double bonds, whereas the hydrophilic part is a polar residue, sometimes charged (e.g., in phosphatidyl choline). The coexistence of these two parts with opposite interactivity with water drives the specific organization called double layer, as represented in Figure 1.1: the arrangement is obtained by two molecules that are placed one in front of the other, and their polar parts are disposed outward facing water.

The double layer can expand until a critical number of molecules are assembled, at the so-called critical aggregation concentration (CAC) that causes the two extremities of the double layer to become close to each other and form a round sphere, with water in its interior. In this way "compartmentalization" occurs, which allows the organization of cellular life to be exploited. In natural membranes cholesterol is the other important lipid component forming part of the layer, with the general effect of modulating the fluidity property of this aggregation. This is not the place to go into a deeper description of the numerous factors influencing membrane formation and its properties, which are better described elsewhere [2–6]. However, it is worth recalling that, as water is the most important element for life, hydrophobicity is the complementary property needed for life organization, which in fact

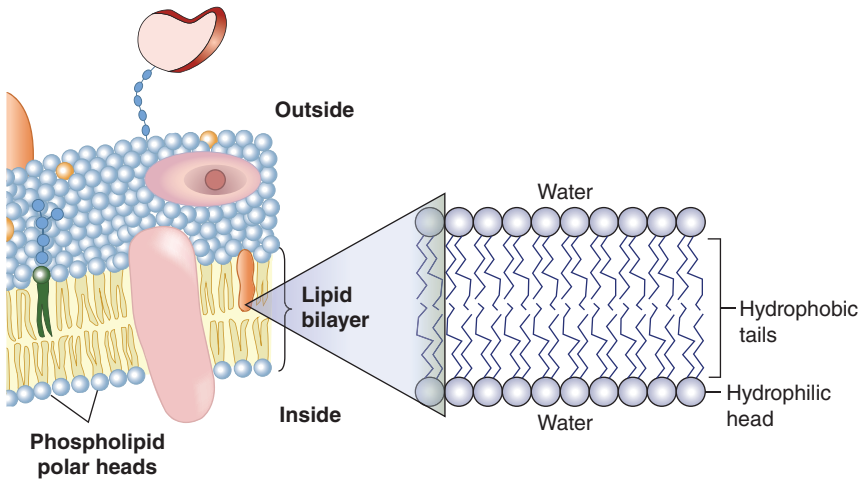

Figure 1.1 The membrane structure made of a double layer of phospholipids, and the fatty acid chains that form the hydrophobic layer

induces compartimentalization. Indeed, the presence of the aqueous and lipid compartments plays a fundamental role in the distribution of the various biological elements, from small molecules to macromolecules, according to their partition coefficient, thus determining their different concentrations, inside and outside cells, by which physical and chemical interactions are established.

The primary function of membranes is to compartimentalize molecules but not to separate them; therefore the regulation of membrane permeability and fluidity properties is studied for understanding the subsequent events of diffusion, exchange, and signaling [7].

In this book we will not study the contribution from the "head" in depth, which is not insignificant, in explaining lipid diversity. In Figure 1.2 the variation of the phospholipid molecules is shown as different tails and heads. As an example, it is worth citing the effects of inositol lipids, which are present in small quantities in membranes; however, they participate in cell signaling associated with growth and immune processes, as well as in programmed cell death, and the transport of chemicals into and out of cells. The protein receptors, after activation, can induce the breakage of inositol lipids into pieces and the phosphate-containing head group (phosphatidylinositol 3-phosphate, PtdIns3*P* or PI3P) released into the cells' interior binds to other proteins, propagating the signal, while the remaining lipid tail is involved in other kinds of binding to proteins, completing the activation process. Glycolipids are also involved in other important signaling processes, such as insulin response, and help the docking of viral proteins (such as HIV virus) or toxins (e.g., cholerae and tetanus toxins) to membranes. They are found in the outward-facing part of the membrane bilayer, and in red blood cells their presence determines the combination of the AB0 blood group a person has. Obviously the distinction of properties and functions of lipids by the polar heads can be deepened by reading several papers on this topic [8, 9].

In this book we focus readers' attention on the hydrophobic tails of the phospholipids composed of fatty acids. This subject will be developed to demonstrate how important these constituents are for health, specifically connecting molecular and nutritional contributions. As shown in Figure 1.2, the fatty acid structures are linked with their carboxylic acid function to the positions C1 and C2 of the L-glycerol moiety of phospholipids. L-glycerol is one of the isomeric forms; therefore it is worth mentioning that nature chose one enantiomer in a similar way as it chose the L-form of amino acids.

The fatty acid chains display a high degree of diversity concerning the carbon atom number (chain length) and the presence of unsaturations

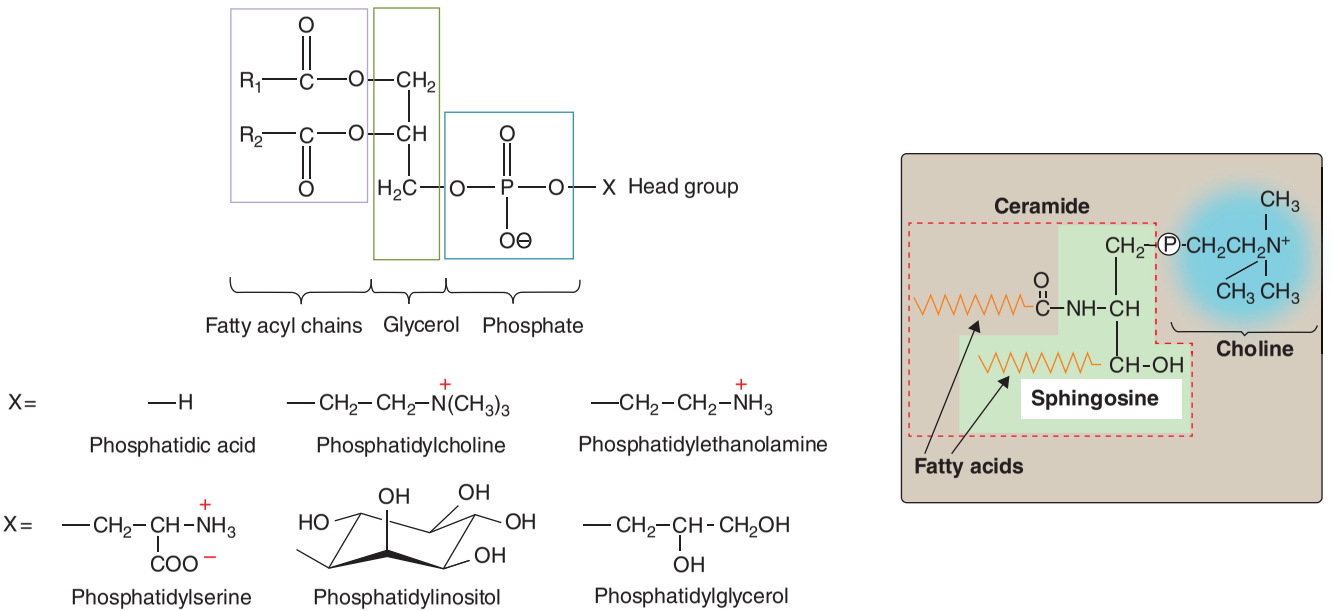

Figure 1.2 Details of the phospholipid molecule with variation of fatty acid tails and polar heads. In the box the structure of sphyngomielin is displayed

(double bonds): (i) the chain can contain from 11 to 25 CH_2 groups plus the carboxylic group (COOH), which is numbered as Carbon-1, and (ii) some of these CH_2 groups can be substituted by CH groups for double bond function in unsaturated lipids. These could appear as small variations, but it is not so. The variability of physical, chemical, and biochemical properties due to chain length and number of unsaturations can be relevant for the effects on membrane fluidity and permeability, as well on its functions.

In Figure 1.3 the main structures and names of the naturally occurring fatty acids in eukaryotic membranes are shown. The trivial names indicate the natural sources where they were first discovered. For the nomenclature, the numbering of the carbon atom chain and indication of the double bonds represent a useful way, together with the specification of the position and geometry of the double bonds, when present.

For example, the nomenclature of 12 : 0 or C12 : 0 indicates a fatty acid with carbon atom chain of 12 and no (0) unsaturation, which belongs to the family of saturated fatty acids (SFA, lauric acid). Conversely, 9*cis*-18 : 1

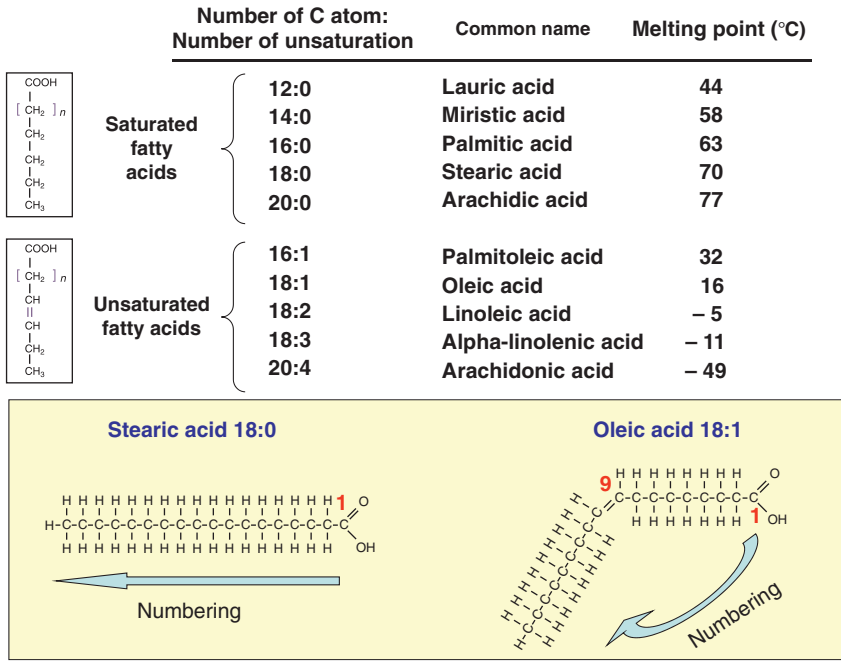

Figure 1.3 List of main saturated and unsaturated fatty acids, with their melting points, trivial nomenclature, and numerical annotation (number of C atoms : number of double bonds)

indicates an 18-carbon atom chain with one double bond in the C9 position with the cis geometrical configuration (starting the numbering from the C1 of the chain), belonging to the family of monounsaturated fatty acids (MUFAs). The positions of the double bond are also described with the notation *delta* Δ followed by the number of the double bond along the chain. For example, in Figure 1.3 oleic acid has the double bond in the Δ. The 18:2 notation corresponds to molecules with two double bonds, and the various structures with more than one double bond belong to the family of polyunsaturated fatty acids (PUFAs). A unifying nomenclature has also been proposed, but the trivial names are still very prevalent. The carboxylic group can be found in the form of carboxylic ester, such as in triglycerides (the C(O)OH group is connected with the OH group of L-glycerol, forming an ester function: C(O)O-glycerol). The carbon atom chain with only CH_2 groups (i.e., numeric notation C12:0) is present in the saturated fatty acid family. The most abundant SFA in the eukaryotic cell membranes is palmitic acid C16:0. In unsaturated fatty acids a carbon atom is connected with another carbon atom by two bonds instead of one, so that in place of two CH_2 groups there is a >CH=CH< functionality, which is in fact the carbon–carbon double bond (Figure 1.4).

As shown in Figure 1.3, the numbering indication is accompanied by the trivial names, which are very much in use despite the efforts of scientists to have a common and unequivocal nomenclature for fatty acids [10], to avoid misunderstanding that are very frequent (i.e., linoleic acid vs. linolenic acid or alpha-linolenic acid vs. gamma-linolenic acid). In Figure 1.3 the melting points are given, which can also be useful for envisaging the wide variety of temperatures realized by the different fatty acid structures. It can be seen that only saturated fatty acids can reach values over the physiological temperature of 37°C, and this can be intuitively extrapolated to the "hardening" effect of saturated fatty acids in the hydrophobic membrane layer. Conversely, the presence of

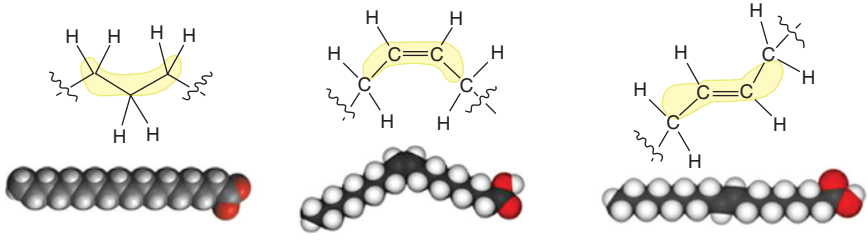

Figure 1.4 A representative region of the carbon atom chain in the saturated fatty acids (left, $–CH_2–CH_2–$ groups), in the cis unsaturated fatty acids (center, with the cis >CH=CH< functionality), and in the trans unsaturated fatty acids

double bonds reduces the melting temperature, which has the effect of "softening" the membrane containing unsaturated fatty acids.

Indeed, the double bond is a very important element of the hydrophobic layer, on which most of the cell membrane characteristics depend. Most of the fatty acids in living organisms (and in eukaryotes, in general) have the double bonds in a precise geometrical configuration, which is called cis (middle structure in Figure 1.4). This corresponds to the position of the two substituents connected to the >CH=CH< group that are in the same direction as the plane involving the double bond. As a consequence, the cis geometry creates a characteristic bent of about 30° in the unsaturated fatty acid chain, compared to saturated fatty acids, which have a typical linear molecular structure. The other possible disposition of substituents is the trans configuration, where the two substituents are in an opposite direction to the double bond plane. As shown in Figure 1.4, the fatty acid structure consequently looses the kink, becoming more similar to the saturated fatty acids. Considering the two types of double bond configurations and the fact that the trans geometry is the most thermodynamically stable one, it is remarkable that the most stable unsaturated isomer is excluded from the natural lipid structures of eukaryotes. The reasons for this exclusion have been considered only recently, based on its evolutionary meaning, since both cis and trans geometries are present in prokaryotes, and the geometrical interconversion via enzymatic activity is the basis of bacterial resistance to stress [11]. Interestingly, the trans lipid structure has a profound effect on membrane fluidity and permeability, as well as on protein and channel functioning, as can be intuitively extrapolated from the sharp difference in the melting points of the corresponding free fatty acids (13.4°C for the 9*cis*-18 : 1 isomer and 44°C for the 9*trans*-18 : 1, whereas the corresponding saturated fatty acid, stearic acid 18 : 0, melts at 72°C) [12]. Indeed, the trans configuration has a completely different effect on the fluidity of the phospholipid bilayer, compared to the cis or saturated one at physiological temperature, and also on its overall sensor functions [11, 13, 14]. The replacement of one cis acyl chain by a trans fatty acid in phosphatidylethanol amine increases the transition temperature in the range of 18–31°C, depending on the structure of the other acyl chain of the lipid molecule. Therefore, the conversion of cis unsaturated fatty acids into their trans configuration results in a significant reduction in membrane fluidity, which is, however, intermediate with the replacement of cis by saturated fatty acids.

The trans geometry has an important role in fat dietary consumption, which became a hot topic in the nineties after the discovery that trans isomers

are found in oils chemically manipulated by the food industry, in particular deodorized and partially hydrogenated oils. In the following years, due to the strong involvement of consumers' organizations especially in the United States, and to scientific research on the health effects of the trans fatty acids (increasing cardiovascular risk, in primis), the US laws became very strict with the obligatory indication of trans fatty acids cited as nutritional facts and a limit of 0.5% of these fats in foods [15]. Nowadays, the food industry seeks different ways to abandon the process of partial hydrogenation and the use of partially hydrogenated oils. In Europe, the control of trans fatty acids in foods and the need for limiting the dietary intake are considered as important issues for the protection of consumers, but disclosure of nutritional information indicating trans fatty acid content is not yet required by legislation. Therefore, their presence in foods of European countries remains unknown (see also Section 4.1). This can be a problem especially because the deodorization process is largely applied when the natural sources of omega-3 fish oils, for example, have to lose their unpleasant smell for entering the functional food chain, such as in milk or margarines. This process employs high temperatures and under these conditions a certain percentage of the cis omega-3 fats are transformed into their corresponding trans isomers, which can also be metabolized to membrane lipids, thus reaching the level of mitochondria and causing functional impairment [16]. From the data obtained so far on the effects of trans fatty acids, it is clear that it is much safer to use only natural, unprocessed oils for food. Moreover, in the market for "healthy" foods, omega-3 fats are perceived by consumers as useful compounds; therefore the use of deodorized fish oils containing trans modifications can belie expectations. The issue of omega-3-containing products, including nutraceuticals, is still only at the level of research, but it is hoped the interest of producers regarding consumer safety can be kindled.

It is worth noting at this point that in recent years the presence of trans isomers has been evidenced not only in connection with diet and oil manipulation, but also with the process of endogenous transformation of natural lipids, due to free radical production during cellular stress [11]. In Figure 1.5 the reaction of sulfur-centered radicals is shown, which are able to enter the hydrophobic layer of the membrane and react with the double bond of unsaturated lipids, thus effecting the reaction of cis–trans isomerization. In Chapter 4, this reactivity will be more detailed, and the role of trans lipids as markers of endogenous stress will be explained. The source of trans lipids as a result of an endogenous transformation of the naturally occurring cis lipids has a different implication compared to nutritional (exogenous) sources, connected

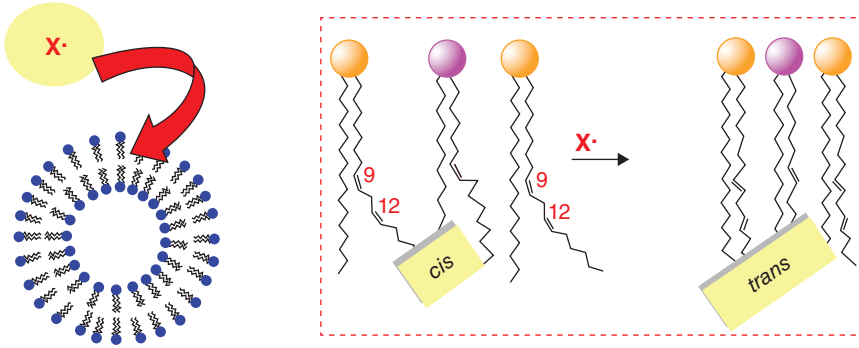

Figure 1.5 Free radical attack (X•) in the membrane bilayer and formation of trans phospholipids

with oxidative pathways as a signaling activity and with a threshold for damage consequences.

1.2 ORGANIZATION AND HOMEOSTASIS

The membrane hydrophobic bilayer has a precise distribution of the fatty acid molecular functionalities, which can be evaluated by computer simulation [4, 17]. As shown in Figure 1.6 the double bond of monounsaturated fatty acids is calculated to occupy the core region of the membrane at ±10 Å from the center in a membrane model whose thickness is about 60 Å. These models bring attention to the important feature of organization that the phospholipid molecules achieve in natural membranes, connected with other facts such as the insertion of protein structures, resulting interactions, and the overall functioning of the membrane, which acts more as a passage of nutritional and signaling substances than as a wall separating the internal and external cellular compartments.

To understand in depth this organization the fundamental unit of the membrane structure has to be described, which is the phospholipid shown in Figure 1.7. It has an amphipatic character, with a polar portion (the "head") and an apolar portion (the "tail" with two hydrophobic fatty acid chains) in the same molecule. The molecular shape can be assimilated to a cylinder, and in aqueous systems a certain number of these molecules spontaneously organize themselves in order to expose only the polar heads toward water, whereas the hydrophobic tails are one in front of the other preventing water contact. In this way the double layer is formed and at a critical aggregation concentration (CAC),

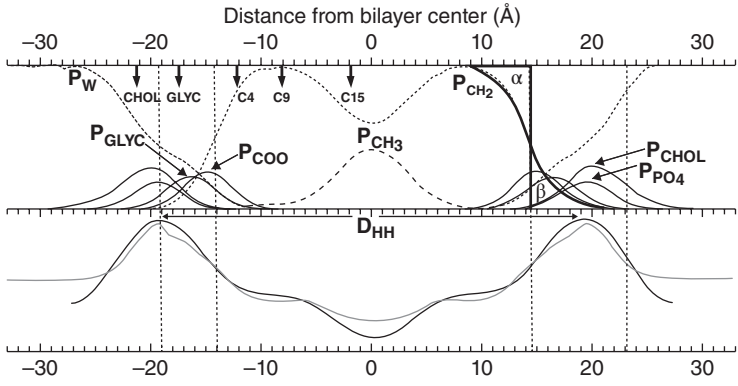

Figure 1.6 Model of the distribution of the structure of phospholipid chain within the membrane bilayer; P= position, D= distance, GLYC= glycerol, COO= ester group, Cn= various position of the fatty acid chain, PO4= phosphate group, CHOL= cholesterol, W= water
Adapted from Ref. [4]

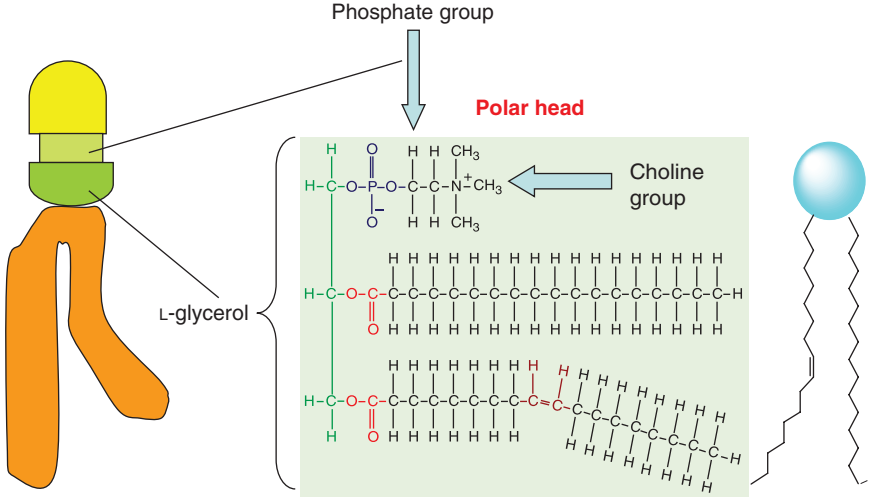

Figure 1.7 A representative phospholipid, with the polar head of phosphatidylcholine and the two fatty acid hydrophobic tails attached to L-glycerol

calculated as the number of molecules per liter of solvent (molarity), the double layer folds on itself forming a spherical form, enclosing an internal volume of water. This effect, called "compartimentalization" in biology, is considered the basis for all life, since the cells are formed only when the membrane is formed, and without the definition of internal/external compartments life cannot start.

In the life of any organism, cells are formed, stay alive for a certain period of time, and then die, whereas new cells are formed during cell turnover in a continuous flow. In the turnover the assembly of phospholipids in a double layer to form the cell membrane is a fundamental aspect. What kind of phospholipids and fatty acids do form the cell membrane? When an *in vitro* experiment on membrane formation is carried out, phospholipids with all types of structures (saturated, cis or trans fatty acids) can form membranes, with the fatty acid residues having a particular influence on vesicle shapes and the resulting volumes, expressed as diameter of the vesicle [13]. In model vesicles, the cell size follows the fatty acid order of saturated < trans < cis, indicating that the latter geometry provides the largest cell volume. This is an important property of cis fatty acids necessary for the eukaryotic cells, which are larger cells than other organisms.

A different consideration must be done in case of *in vivo* formation of natural cell membranes, when the compartmentalization by the aggregation of phospholipids is crucial not only for the formation of the compartment, but also to produce the functionalization of the double layer with a series of proteins, which allow signaling and exchanges to occur. It is now known that the selection of different fatty acids of the membrane phospholipids is connected with the nature of the proteins that are formed in the cell according to the genetics of the cell line. In other words, tissues are composed of cell membranes containing variable quantities of fatty acids depending on the type of tissue and its function. In Chapter 2 the fatty acid families and the levels of different tissues will be treated in depth.

Here we would like to remark that when cells are formed or replicate, there is an enlargement of the cell volume and a duplication of the number of phospholipids, parallel to DNA duplication; therefore the recruitment of fatty acids for new phospholipids is needed (Figure 1.8). The availability of fatty acids from the lipid pool of each individual becomes a crucial point during cell turnover (see also Section 3.3).

In fact, the selection of fatty acids for cell membranes is effected on the basis of the available fatty acid pool, which in turn is connected to the metabolism and the diet of the individual. As will be described in the next chapter, fatty acids come from an integrated contribution of biosynthesis and nutrition, to achieve an adequate diversity in the fatty acid pool. For eukaryotes this availability is crucial, especially because some fatty acids like omega-6 and omega-3 fatty acids cannot be biosynthesized, and in fact are called essential fatty acids. During the fatty acid recruitment for the formation of cell membranes, the more complete and balanced the

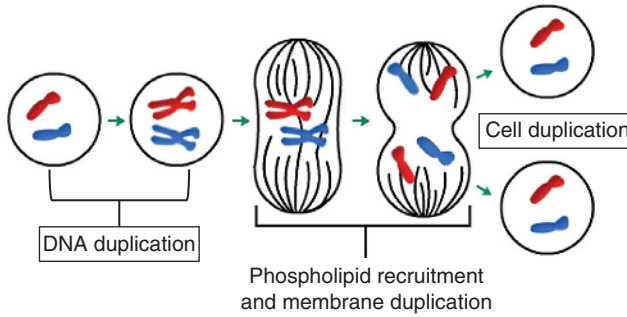

Figure 1.8 Duplication of membranes during cell replication

fatty acid pool, the better the resulting membrane composition. Membranes can become an important observational point for personalized evaluation. In case of incompleteness of the fatty acid pool, membranes of the tissues are formed with an improper fatty acid balance compared to the standard values, and this corresponds to a wrong assembly from a biological point of view with impairment of membrane functionality.

However, the event of membrane impairment is not so dramatic initially to be noticed, because the membrane composition is very dynamic and undergoes continuous modifications, which have been the subject of intense research in the last two decades. The model of fluid mosaic envisaged by Singer and Nicholson in 1978 has been integrated with new knowledge on the processes of membrane remodeling and signaling, which imply continuous lipid changes. These processes will be considered in detail in Chapter 5. Here it must be mentioned that once the composition of the membrane compartment is established, the process of phospholipid remodeling takes place every moment as a response to any stimulus and the changes in the membrane composition are part of cell adaptation. The fatty acid selection for the membrane phospholipids after each stimulus represents the "molecular" response combined with the quality of the lipid pool. It is now well known that the regulation of this process is based on the principle of "homeostasis" (or homeoviscous adaptation), by which membranes after perturbation restore, or at least try to restore, their balance keeping all functions as constant as possible. This includes also the functioning of proteins embedded in the membrane structure; therefore, successful homeostatic control is reflected by the efficacy of the metabolic response to stimulus.

At this point it is worth underlining the fundamental link between the molecular aspect and the clinical outcome, which is of interest to health operators for improving the diagnostic interpretation of the individual

status. Indeed, if the phospholipid selection during the earlier-mentioned remodeling cannot occur in the proper way, the resulting homeostatic control is lost, and this can be reflected by a wrong cellular response with several symptoms, without representing a real pathological status. Membrane lipidomics provides information on the role of membranes for the homeostatic control as a fundamental molecular aspect for health. Based on the membrane asset and its homeostatic control, the cell adaptation to physical (pH, ionic changes, temperature, etc.) and biochemical (signal cascades, inflammation, stress, etc.) solicitations takes place, that has to occur instantaneously, with the final goal to harmonically follow up cellular events.

Therefore, cell homeostasis is based on "molecular" homeostasis obtained not only by retaining the properties of fluidity and permeability, but mainly by allowing the rapid exchange of its lipid elements as a short-term response. On the basis of recent discoveries, it can be concluded that membrane organization has a key role in the regulation and balance of the whole cellular metabolism, which can deeply influence life. The definition of "membranes as metabolic pacemaker" from Professor Antony Hulbert of the University of Wollongong, Australia, indicates that membranes are not a passive spectator but an active element of cell life and fate [18].

1a In Depth: The Formation of a Cell Membrane

The formation of the membrane double layer is a fundamental biological phenomenon, which has inspired an important application in biotechnology, which is called liposome. As per Danilo Lasic, one of the scientists that first developed this field [19], "every cell on the planet is surrounded by a membrane that has the same basic lipid bilayer structure as that exhibited by liposomes." The property of spontaneous aggregation exhibited by phospholipids was carefully studied, observing the typical behavior of these amphiphilic molecules, as shown in Figure 1.9. The mode of aggregation in an aqueous medium is the same for all types of phospholipids, whose molecular shape can be assimilated into a cylinder, therefore forcing the organization in a layer growing on the lateral sides. Since the molecules are amphipatic, the hydrophobic tails cannot face the water and one layer becomes closer to another layer, in such a way that the hydrophobic parts are in the inner part of the layer, avoiding water contact, whereas the polar heads can be exposed to water. The so-formed double layer continues to grow until the molecules reach a "critical" number (CAC, critical aggregation concentration) such that the bilayer folds on itself, thus creating a vesicle with a cavity full of water surrounded by water. In biology this is the cell prototype (protocell); in biotechnology this is called liposome (Figure 1.9).

The diversity of fatty acids composing phospholipids and the role of cholesterol as the "additive" of this lipid assembly attracted considerable interest from researchers, since they certainly take part in the efficiency and regulation of membranes. An investigation of liposome behavior provided numerous insights on membrane behavior and biological effects.

It is also clear that the membrane lipid library (about 1000 molecules up to now) combined with the membrane protein structures discovered so far (among about 71 000 protein structures available in the RSCB Protein Data bank, 1 095 structures are those of membrane proteins) define a larger field of lipid–protein interactions still to be thoroughly explored [3], in order to figure out what are the important elements needed during membrane formation and reduce the possibility of functional impairment.

Definitely, if the DNA organization and its four bases describing the genetic code involved incredible efforts in terms of financial

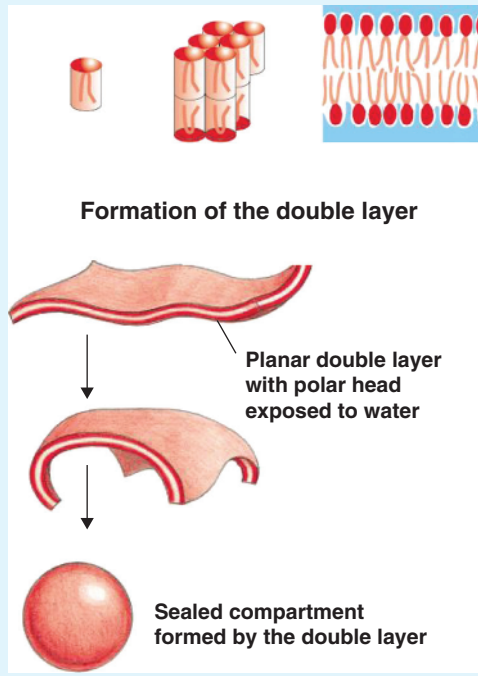

Figure 1.9 Aggregation process of the phospholipid into a double layer, with folding and creation of the proto-cell or a liposome

and human resources, it is not easy to figure out how much involvement of money and researchers would be needed to unveil the "membrane code."

As will be seen in Chapter 2, the simplest principle to be followed for optimal membrane performance is the completeness of the "fatty acid pool," in quantity and quality of the fatty acid molecules, thus allowing the membrane formation process to occur with the spontaneity and self-regulation used during millions of years of life experience!

1b In Depth: Cholesterol and Membranes

Cholesterol is a lipid molecule that can occupy the upper region of the bilayer, intercalating the phospholipids and increasing the space between them. Actually, recent research highlighted that the position and orientation of phospholipid/cholesterol membranes

follows precise rules driven by the polar (OH group) and apolar (steroid ring and alkyl chain) molecular portions, avoiding the cholesterol–cholesterol direct contact, but mostly intercalating cholesterol between two phospholipids as in Figure 1.10 [20, 21].

The cholesterol effect is the increase of membrane fluidity; therefore the lower the fluidity, the higher the quantity of cholesterol required. Reduced fluidity occurs when the saturated fatty acid proportion exceeds the optimal values of the overall content of membrane phospholipids. This condition is in general due to an activation of biosynthesis (FAS, fatty acid synthase), as an endogenous process, or an increased intake of food rich in saturated fatty acids, as an exogenous source. The homeostatic regulation of fluidity with the increase of saturated fats brings to the biosynthesis of cholesterol as feedback. Since the value of cholesterol in the plasma is monitored as a preventive indicator of metabolic unbalance, it is very important for health operators to acquire a comprehensive scenario of the "molecular" factors influencing this biomarker, where the membrane properties must be taken into account due to the contiguity between lipids and cholesterol (Figure 1.10). On the other hand, the feedback of cholesterol biosynthesis can also be induced by an excess of membrane fluidity, when stabilization of the membrane assembly is needed. This can occur when an excess of PUFA is incorporated in the bilayer and destabilizes the membrane asset. This aspect will be discussed in the section dedicated to nutraceuticals in Part 2.

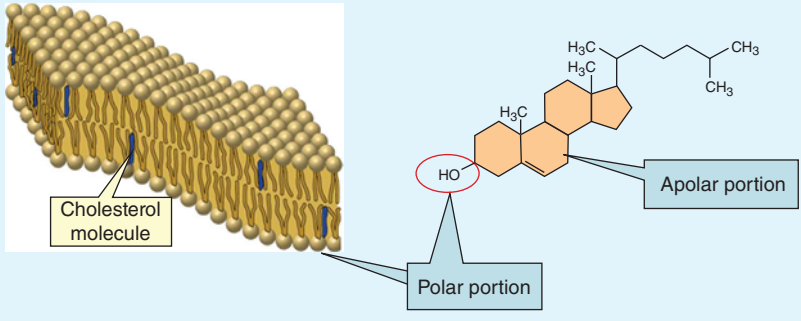

Figure 1.10 Cholesterol and its position in membranes

Obviously, dietary factors have to be carefully considered and all aspects can vary due to the individual situation. As a general rule, among the factors influencing cholesterol levels, saturated fatty acids have a relevant effect and this cannot be dissociated from the previously examined effect on membrane properties. Indeed, it is well known that the diminution of saturated fatty acids from the diet lowers plasma cholesterol levels [22]. The correlation between cholesterol and saturated fatty acid levels should represent a seminal example of the application of "molecular" principles to the definition of a comprehensive "health biomarker," giving to health operator an important piece of information about the dietary and metabolic status of the subject. In the medical practice discussed in Part 2, a panel of fatty acid bioindicators will be included in order to set up nutritional and nutraceutical strategies directed toward the correct membrane balance.

1c In Depth: Lipid Rafts

In membrane organization an important role was discovered for the so-called lipid rafts, which are small aggregates of phospholipids and cholesterol, containing another type of phospholipid called sphingolipid (see Figure 1.2). A mixture of these three types of lipids creates a rigid packing with less lateral movement or diffusion, corresponding to microdomains existing in a liquid-ordered phase that is significantly more fluid than a gel phase. This is quite different from the phospholipid liquid phase; therefore such a lipid mixture separates as "raft," generally of small size (26–70 nm in diameter) floating in the double layer. Lipid rafts can be isolated from the rest of plasma membrane since they constitute a "detergent-resistant" section of the lipid bilayer. The name describes this phenomenon, which is very important for the accommodation of specific macromolecules, that is, proteins of specific size, and this makes the compartimentalization of the membrane even more precise, regarding separation of places and roles [23]. Lipid rafts can be isolated from the rest of plasma membrane since they constitute a "detergent-resistant" section of the lipid bilayer; however, research is still ongoing on the existence and role of lipid rafts. It emerged that rafts are involved in the movement of cholesterol and

other proteins, thus furnishing organized places for signaling, or as the points for molecules to leave and to enter cells, even in the viral or microorganism attack (such as HIV or malaria) through also the attachment of glycolipids to rafts. This subject can be considered "in progress" and more knowledge will be gathered in the coming years for explaining completely the meaning of the membrane organization and the effective contribution of lipid rafts.