Multi-author Review

Assembly of lipids into membranes

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Introduction

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Biological membranes consist of two major components: lipids and proteins. According to the classical model of Singer and Nicolson [5], membrane lipids form a bilayer; proteins are embedded in the membrane and/or protrude into the aqueous environment. Among the membrane-forming lipids, glycerophospholipids are the quantitatively most prominent, followed by sterols, sphingolipids and glycoglycerolipids. Membrane-forming lipids such as glycerophospholipids are amphiphilic molecules; their polar groups are oriented towards the aqueous environment, and their hydrophobic tails form the apolar core of the membrane. Sterols intercalate into the phospholipid bilayer, and can reinforce membranes by virtue of their molecular structure (conjugated ring system). Glycolipids, with their very hydrophilic carbohydrate moiety and variability of structure, are especially well suited for processes involving the interaction of membrane surfaces with components of the surrounding aqueous compartments. Triacylglycerols, sterol esters and free fatty acids are only minor components of organelle membranes. The major location of triacylglycerols and sterol esters is in the lipoprotein fraction of the blood and in storage particles within the cell; they thus provide an energy reserve (fatty acids) or a pool of precursors (fatty acids, sterols), which can be mobilized for membrane biosynthesis.

Specific functions of lipids are only in part understood. Besides their ability to form membranes, and thereby to contribute to the compartmentalization of a cell, lipids are able to interact with membrane enzymes and thus regulate their activity. Alterations of the lipid composition of a membrane may result in changes of physicochemical properties and in modulation of the activity of enzymes in the membrane environment. Recently, it has been recognized that lipids and their degradation products function as second messengers in signal transduction across the plasma membrane.

Cells can be supplied with membrane lipids in two different ways. Firstly, cells are able to take up lipids from the extracellular space. This pathway applies especially to mammalian cells, which interact with lipoproteins of the blood stream. The reverse can also occur; cellular lipids are assembled into lipoproteins, which are then secreted into the circulation. Secondly, cells can synthesize their own lipids. It has to be pointed out that not all the membranes of a cell have the same capacity for lipid synthesis. Although activities of lipid synthesizing enzymes have been detected in a number of cellular membranes, the endoplasmic reticulum is generally accepted as the major cellular site of lipid biosynthesis. Certain membranes (e.g. mitochondria) synthesize lipids only to a minor extent, whereas other membranes (e.g. the plasma membrane) obviously lack this ability completely.a This situation necessitates the supply of many cellular membranes with lipids that have originated in other compartments. Efficient processes are necessary to transfer lipid molecules from their site of synthesis to their final destination (for recent reviews see refs 1, 2, 6, 7).

Several mechanisms of intracellular lipid transport are discussed. 1) Lateral diffusion of lipids. The transport of lipid molecules occurs within the plane of a membrane bilayer; membrane contact between organelles leads to membrane fusion and translocation of membrane lipids from one membrane to the other. 2) Vesicular transport of lipids. Vesicles containing lipids to be transported bud off one organelle and migrate to another membrane, where fusion leads to delivery to the target membrane. 3) Transport of monomeric lipids. This type of translocation of lipid molecules through an aqueous compartment can either occur spontaneously, or with the aid of lipid transfer proteins (formerly termed lipid exchange proteins). 4) Transbilayer movement of lipids. Insertion of lipids into a preexisting membrane or synthesis on one side of the membrane leads to a specific transmembrane orientation [4]. In order to reach the opposite leaflet of the membrane bilayer, lipids have to traverse the membrane. Evidence exists that certain lipids are spontaneously translocated across membranes, whereas others need protein catalysis by so-called flippases [3] for their transmembrane movement.

Proteins as well as lipids have to migrate between cellular organelles. Although the target membranes are the same, marked mechanistic differences exist between the migration processes of these two types of molecule. Due to their relatively low molecular mass, lipids show a much

faster lateral diffusion within the plane of a membrane, and more rapid intermixing than proteins. Proteins are destined for very specific locations (organelles) within the cell, whereas differences in the lipid composition between organelle membranes are not absolute. All organelle membranes contain more-or-less the same lipid classes, and only the ratio between these classes is unique and characteristic for a certain subcellular fraction. Finally, proteins contain signal sequences, which recognize the target membrane (e.g., via a specific receptor). No such signals exist in lipid molecules, which raises the question of the mechanism(s) of sorting of lipids within the cell. Investigations over the last 20 years have shown that lipid flux is a very complex process. It is very likely that different mechanisms of intracellular lipid transport exist in parallel, probably in most types of cells. Lipid transfer processes have been studied intensively with mammalian cells, but plant cells have also been used successfully for this purpose, and it is another area in which microorganisms have proved to be useful model cells. Most of our knowledge about lipid transfer processes and mechanisms comes from experiments in vitro. It is a matter of dispute which of these mechanisms are of relevance in vivo, and what contribution is made by each individual mechanism to membrane biogenesis and assembly. The present Multi-author Review gives an overview of lipid transport in various types of cells, the transport routes of the major classes of lipids, the mechanisms involved in intracellular lipid traffic, and the migration of lipids between cells and lipoproteins. The authors discuss these events and their contribution to the assembly of lipids into biological membranes.

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1 Bishop, W. R., and Bell, R. M., Assembly of phospholipids into cellular membranes: biosynthesis, transmembrane movement and intracellular translocation. A. Rev. Cell Biol. *4* (1988) 579–610.
2 Dawidowicz, E. A., Dynamics of membrane lipid metabolism and turnover. A. Rev. Biochem. *56* (1987) 43–61.
3 Devaux, P. F., Phospholipid flippases. FEBS Lett. *234* (1988) 8–12.
4 Op den Kamp, J. A. F., Lipid asymmetry in membranes. A. Rev. Biochem. *48* (1979) 47–71.
5 Singer, S, J., and Nicolson, G. L., The fluid mosaic model of the structure of cell membranes. Science *175* (1972) 720–731.
6 Sleight, R. G., Intracellular lipid traffic in eukaryotes. A. Rev. Physiol. *49* (1987) 193–208.
7 Van Meer, G., Lipid traffic in animal cells. A. Rev. Cell Biol. *5* (1989) 247–275.

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Interaction of lipid transfer protein with plasma lipoproteins and cell membranes

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Summary. The hydrophobic lipid components of lipoproteins, cholesteryl ester and triglyceride, are transferred between all lipoproteins by a specific plasma glycoprotein, termed lipid transfer protein (LTP). LTP facilitates lipid transfer by an exchange process in which cholesteryl ester and triglyceride compete for transfer. Thus, LTP promotes remodeling of the lipoprotein structure, and plays an important role in the intravascular metabolism of these particles and in the lipoprotein-dependent pathways of cholesterol clearance from cells. The properties of LTP, its mechanisms of action, its roles in lipoprotein metabolism, and its modes of regulation are reviewed along with recent data that suggest a possible role for this protein in directly modifying cellular lipid composition.
Key words. Lipid transfer protein; lipoprotein metabolism; lipoprotein remodeling; cholesteryl ester; triglyceride.

Plasma lipoproteins

Plasma lipoproteins can be classified into five categories: chylomicron, and very low density (VLDL), intermediate density (IDL), low density (LDL), and high density lipoproteins (HDL). Each class is heterogeneous in composition, reflecting, for the most part, the fact that each fraction contains a collection of particles that are at different stages of their metabolism. Thus, it is important to realize that lipoproteins are not the static structures that are isolated and characterized at a point in time, but rather, they are dynamic particles that reflect the sum of many different events which affect their composition. This review focuses on one of these events.

Generally, the structure of plasma lipoproteins can be divided into two domains – the coat and the core. The coat domain interacts with the aqueous environment and is composed mainly of phospholipid, unesterified choles-