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Review

Lipids of mitochondria

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ABSTRACT

A unique organelle for studying membrane biochemistry is the mitochondrion whose functionality depends on a coordinated supply of proteins and lipids. Mitochondria are capable of synthesizing several lipids autonomously such as phosphatidylglycerol, cardiolipin and in part phosphatidylethanolamine, phosphatidic acid and CDP-diacylglycerol. Other mitochondrial membrane lipids such as phosphatidylcholine, phosphatidylserine, phosphatidylinositol, sterols and sphingolipids have to be imported. The mitochondrial lipid composition, the biosynthesis and the import of mitochondrial lipids as well as the regulation of these processes will be main issues of this review article. Furthermore, interactions of lipids and mitochondrial proteins which are highly important for various mitochondrial processes will be discussed. Malfunction or loss of enzymes involved in mitochondrial phospholipid biosynthesis lead to dysfunction of cell respiration, affect the assembly and stability of the mitochondrial protein import machinery and cause abnormal mitochondrial morphology or even lethality. Molecular aspects of these processes as well as diseases related to defects in the formation of mitochondrial membranes will be described.

Contents

Abbreviations: CDS, CDP-diacylglycerol synthase; CL, cardiolipin (diphosphatidylglycerol); CS, contact sites; DMPE, dimethylphosphatidylethanolamine; ER, endoplasmic reticulum; ERMES, ER-mitochondria encounter structure; IMM, inner mitochondrial membrane; IMS, intermembrane space; MAM, mitochondria associated membrane; MICOS, mitochondrial contact site; MINOS, mitochondrial inner membrane organizing system; MitOS, mitochondrial organizing structure; MLCL, monolysocardiolipin; OMM, outer mitochondrial membrane; PA, phosphatidic acid; PAM, presequence translocase associated motor; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PG, phosphatidylglycerol; PI, phosphatidylinositol; PS, phosphatidylserine; SAM, sorting and assembly machinery; TIM, translocase of the inner membrane; TOM, translocase of the outer membrane.

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1. Introduction

Biological membranes are multifunctional cellular constituents not only protecting the cell from external sources but also assigning specific processes to certain compartments. The main building blocks of most membranes are phospholipids which provide a matrix for embedding proteins, sphingolipids and sterols. Lipids are not randomly distributed among biological membranes. Instead, they are highly specific and characteristic for each organelle influencing their shape, structure and function [1]. A specialized organelle for studying membrane biochemistry is the mitochondrion with its complex structure containing two membranes, the outer (OMM) and the inner mitochondrial membrane (IMM). The strongly folded cristae give rise to two aqueous compartments, the intermembrane space (IMS) and the matrix. Mitochondria are partially autonomous organelles. They harbor their own DNA, RNA and protein synthesizing machinery, but only 1% of their proteins are formed on ribosomes in the mitochondrial matrix whereas the bulk of mitochondrial proteins is encoded by nuclear genes, translated on cytosolic ribosomes and imported into mitochondria [2,3]. Mitochondria are also capable of synthesizing some lipids on their own, but depend at the same time on the transfer and assembly of lipids mainly formed in the endoplasmic reticulum (ER) (for reviews see [4–11]). The continuous supply and exchange of lipids is required for maintaining mitochondrial membrane integrity and overall cellular function.

In this review, we will summarize the present knowledge about lipids of mitochondrial membranes. Characteristic features of the mitochondrial lipid composition compared to other cellular membranes will be addressed. Furthermore, the topology and distribution of lipids in the OMM and IMM as well as asymmetrical arrangement within the bilayer are presented. Central subjects of this article are biosynthesis, regulation and transport of lipids to and between mitochondrial membranes. Possible interactions and functions of mitochondrial lipids with respect to stabilization and assembly of mitochondrial protein complexes involved in respiration, energy production and protein import are discussed. Some aspects of the physiological relevance of mitochondrial lipids will be addressed, but for more details describing these aspects the reader is referred to recent reviews [9,12,13].

2. Lipid composition of mitochondria

Each subcellular compartment of eukaryotes has a distinct set of proteins and lipids with phosphatidylcholine (PC) and phosphatidylethanolamine (PE) being the most abundant phospholipids found in membranes from yeast to mammalian cells (Tables 1–3; and reviews Refs. [5,14,15]). In contrast to these bulk phospholipids, enrichment of phosphatidylserine (PS), sterols and sphingolipids is specific for the plasma membrane and the Golgi apparatus which also contains higher amounts of phosphatidylinositol (PI); and accumulation of sphingolipids is specific for lysosomes whereas chloroplasts display an elevated phosphatidylglycerol (PG) content.

Mitochondria from different cell types share the following specific characteristics: (i) Phospholipid to protein and sterol to protein ratios are low compared to other subcellular fractions. (ii) PC and PE are the major phospholipids which account for about 80% of total phospholipids. (iii) Mitochondria have high cardiolipin (CL) content in the range of 10–15%. (iv) Sterols and sphingolipids are only found at low amounts (see Tables 1–3). In different mammalian cells and tissues, the mitochondrial lipid composition is more or less identical (Table 1). Exceptions are mitochondria from heart, brain, kidney, adrenal cortex and spleen which additionally contain PC and PE plasmalogens in the range of 5–30% of total phospholipids (for recent reviews see Refs. [16,17]). Plasmalogens are a class of phospholipids carrying a vinyl ether bond in the *sn-1* and an ester bond in the *sn-2* position of the glycerol backbone. This structure leads to strong lipophilic properties and allows plasmalogens to form inverse hexagonal phase structures, thereby favoring membrane fusion [18,19]. Depending on the tissue, plasmalogens are important for the function of transmembrane proteins and membrane-related intracellular and extracellular cholesterol transport [19–22]. Mammalian cells and cell lines like Morris hepatoma, Zajdela hepatoma, Hepatoma from rat and mouse and Fibroblasts (mouse, BHK) contain sphingolipids in the range of 1–12% of total phospholipids, whereas mitochondria of microorganisms and plants are devoid of this lipid class (for recent review see Ref. [23]). Classical lipid analysis using conventional methods as described in some of the above mentioned review articles were confirmed and extended by recent lipidome analyses

Table 1
Lipid composition of subcellular fractions of rat liver.

	Mitochondria	Endoplasmic reticulum	Lysosomes	Golgi	Plasma membrane
Phospholipid (mg/mg protein)	0.175	0.374	0.156	0.825	0.672
Sterols (mg/mg protein)	0.003	0.014	0.038	0.038	0.128
	% of total phospholipids				
Phosphatidylcholine	44	60	48	51	40
Phosphatidylethanolamine	34	23	17	21	24
Phosphatidylinositol	5	10	6	12	8
Phosphatidylserine	1	2	3	6	9
Cardiolipin	14	1	1	1	1
Phosphatidic acid	<1	1	1	<1	1
Sphingomyelin	1	3	24	8	17

Data from Daum and Vance [5].