Biochimica et Biophysica Acta xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

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

Effects of lipids on mitochondrial functions☆

Christoph U. Mårtensson [a,b], Kim Nguyen Doan [a,b], Thomas Becker [a,c,*]

[a] Institute for Biochemistry and Molecular Biology, ZBMZ, Faculty of Medicine, University of Freiburg, 79104 Freiburg, Germany
[b] Faculty of Biology, University of Freiburg, 79104 Freiburg, Germany
[c] BIOSS Centre for Biological Signalling Studies, University of Freiburg, 79104 Freiburg, Germany

ARTICLE INFO

Article history:
Received 13 May 2016
Received in revised form 16 June 2016
Accepted 21 June 2016
Available online xxxx

Keywords:
Mitochondria
Cardiolipin
Respiratory chain
Protein import
Mitochondrial dynamics

ABSTRACT

Mitochondria contain two membranes: the outer and inner membrane. Whereas the outer membrane is particularly enriched in phospholipids, the inner membrane has an unusual high protein content and forms large invaginations termed cristae. The proper phospholipid composition of the membranes is crucial for mitochondrial functions. Phospholipids affect activity, biogenesis and stability of protein complexes including protein translocases and respiratory chain supercomplexes. Negatively charged phospholipids such as cardiolipin are important for the architecture of the membranes and recruit soluble factors to the membranes to support mitochondrial dynamics. Thus, phospholipids not only form the hydrophobic core of biological membranes that surround mitochondria, but also create a specific environment to promote functions of various protein machineries. This article is part of a Special Issue entitled: Lipids of Mitochondria edited by Guenther Daum.

1. Introduction

Mitochondria are essential for survival of eukaryotic cells since they exert multiple biochemical functions including ATP production via the oxidative phosphorylation, synthesis of amino acids, heme, lipids and the biogenesis of iron sulfur clusters. Defects of mitochondrial functions and biogenesis can lead to the development of severe diseases [1,2]. Mitochondria emerged by an endosymbiotic event two billion years ago, in which a eukaryotic ancestor cell incorporated an α-proteobacterium-like prokaryote. The prokaryotic cell was not digested, but instead evolved to a cell organelle, the mitochondria [3,4].

The presence of two surrounding membranes, the outer and inner membrane, is reminiscent of the endosymbiotic origin of mitochondria. The two membranes give rise to two aqueous compartments: the intermembrane space and mitochondrial matrix. Mitochondrial membranes exhibit features and specific functions that set them apart from other cellular membranes. First, they contain mainly phospholipids, whereas only trace amounts of sterols and sphingolipids are present except in cells that synthesize steroid hormones [5–8]. Second, a hallmark of mitochondria is the high content of cardiolipin (CL), which was inherited from the prokaryotic endosymbiont [5–8]. Third, the inner membrane contains an unusual high load of proteins. The majority of these proteins like subunits of the respiratory chain complexes, the F_1F_O-ATP synthase and carrier proteins are involved in oxidative phosphorylation [1,2,9]. Fourth, mitochondria undergo constantly fusion and fission to allow exchange of their content including the mitochondrial DNA, which is crucial for maintaining the respiratory energy metabolism. Such processes involve transient rupture of the classical bilayer structure of the membranes and mixing of the phospholipid content [10,11]. In mitochondria the fusion and fission of two membranes have to be coordinated. Fifth, the inner membrane is spatially divided into inner boundary and cristae membrane. Cristae are large invaginations, where the respiratory chain complexes are localized. Consequently, the inner membrane contains bended membrane regions including crista junctions and crista tips. Cristae can undergo massive remodeling to allow release of cytochrome *c* during apoptotic signalling [12]. Other specific regions of the inner membrane form contact sites to the outer membrane and differ in protein and lipid composition [6,13,14]. Sixth, due to their endosymbiotic origin mitochondria have a complex system of protein sorting and assembly pathways. The vast majority of mitochondrial proteins are synthesized as precursors on cytosolic ribosomes. These precursor proteins are imported into the organelle and subsequently sorted to the different subcompartments by protein translocases [15–19]. Additionally, mitochondria contain a small circular DNA encoding for eight proteins in baker's yeast *Saccharomyces cerevisiae* and thirteen proteins in humans.

Abbreviations: CL, cardiolipin; PE, phosphatidylethanolamine; PC, phosphatidylcholine; PS, phosphatidylserine; PI, phosphatidylinositol; PA, phosphatidic acid; PG, phosphatidylglycerol; CDP-DAG, cytidine diphosphate diacylglycerol; TOM, translocase of the outer membrane; TIM23, presequence translocase; TIM22, carrier translocase; PAM, presequence translocase-associated motor; SAM, sorting and assembly machinery; MIM, mitochondrial import machinery; MIA, mitochondrial intermembrane space import and assembly; OXA, oxidase assembly; ERMES, ER-mitochondria encounter structure; Dnp1/DRP1, dynamin related protein; MFN, mitofusin; Mgm1, mitochondrial genome maintenance; MICOS, mitochondrial contact sites and cristae organizing system.

☆ This article is part of a Special Issue entitled: Lipids of Mitochondria edited by Guenther Daum.

* Corresponding author at: Institute for Biochemistry and Molecular Biology, ZBMZ, Faculty of Medicine, University of Freiburg, 79104 Freiburg, Germany.
E-mail address: thomas.becker@biochemie.uni-freiburg.de (T. Becker).

http://dx.doi.org/10.1016/j.bbalip.2016.06.015
1388-1981/

These proteins are mainly components of the respiratory chain. Specific protein factors mediate their assembly with nuclear-encoded subunits into functional protein machineries [20,21]. Thus, mitochondrial membranes provide an optimal environment for protein transport and assembly processes.

The proper lipid composition of the membranes is crucial for membrane-bound protein machineries to maintain mitochondrial biogenesis and functions (Fig. 1). Particularly, CL is important for the stability and activity of mitochondrial protein machineries and membrane dynamics [22–24]. In this review we will summarize current findings of the functions of lipids in protein import, oxidative phosphorylation, fusion and fission of the organelle, architecture and organization of membranes [6,25–29]. For a detailed description of the role of lipids in apoptosis and mitophagy we refer to two other reviews of this special issue [30,31]. Thus, in addition to building up the lipid-bilayer of the membrane phospholipids affect central processes for mitochondrial biogenesis, function and dynamics.

2. Mitochondrial lipids and their biosynthesis pathways

Phosphatidylcholine (PC) and phosphatidylethanolamine (PE) are the major phospholipids in mitochondria representing 40–45% and 25–30%, phosphatidylinositol (PI) and cardiolipin (CL) account for 10–15% and phosphatidylserine (PS) for 3–5% of the total mitochondrial lipid content in yeast, mammalian and plant cells [5–8]. Phosphatidic acid (PA) and phosphatidylglycerol (PG) are precursors of other phospholipids like CL and present in minor amounts. The composition of outer and inner mitochondrial membrane differs greatly. The outer membrane has one of the lowest protein contents in cellular membranes, whereas the inner mitochondrial membrane is particularly rich of proteins [6]. CL is highly enriched in the inner membrane, whereas only about one quarter of the total mitochondrial CL is present in the outer membrane [8,32,33]. Mitochondrial membranes have a high content of so-called non-bilayer forming phospholipids like PE and CL. While bilayer forming phospholipids like PC, PI or PS have a headgroup and acyl chains of a similar diameter, the headgroup of non-bilayer forming phospholipids has a smaller diameter than the bulky fatty acid-tail (Fig. 2). Depending on pH and the presence of divalent cations these conical shaped phospholipids are prone to form non-bilayer structures like the hexagonal II phase when isolated. According to current models the presence of these phospholipids can locally induce membrane curvature and destabilization of the lipid bilayer to facilitate crucial processes like membrane fusion or protein insertion [5,34]. The importance of these non-bilayer forming phospholipids for mitochondrial functions is reflected by the observation that simultaneous loss of mitochondrial PE and CL biosynthesis is lethal for the yeast cell [35].

Mitochondria are capable of synthesizing CL and PE, while the biosynthesis of other phospholipids takes place in the endoplasmic reticulum (ER) (Fig. 3). The biosynthesis pathway of the dimeric phospholipid CL has been well characterized in yeast mitochondria (Fig. 3A). It starts with the conversion of PA to cytidine diphosphate diacylglycerol (CDP-DAG) by Tam41 [36]. Subsequently, the phosphatidylglycerolphosphate synthase (Pgs1) combines CDP-DAG with glycerol-3-phosphate to form phosphatidylglycerolphosphate (PGP) [37]. Gep4 dephosphorylates PGP to form PG [38]. The cardiolipin synthase (Crd1) catalyzes the reaction of PG with a second molecule of CDP-DAG to produce premature CL [39,40]. To form the mature CL, which usually contains four linoleic acids, remodeling of the acyl chain composition takes place. The phospholipase Cld1 removes one acyl chain producing monolysocardiolipin (MLCL) [41]. Subsequently, the transacylase Taz1 transfers an acyl chain from a second phospholipid like PC to MLCL to form the mature CL [42,43]. Whereas the first biosynthesis steps occur at the matrix side of the inner membrane, Taz1 associates with the outer and inner membrane to conclude remodeling of CL [26,30,44,45]. Major steps of the biosynthesis of CL are conserved in mammals [8,26]. Mutations of the human Taffazin, the homologue of yeast Taz1, have been linked to the Barth syndrome, a disease characterized by neutropenia, dilated cardiomyopathy, skeletal myopathy, growth retardation and 3-methylglutaconic aciduria [46–48]. Additionally, two further enzymes contribute to CL remodeling in mammalian mitochondria: the inner membrane associated MLCL acyl-transferase (termed MLCLAT1) [49] and acyl-CoA:lysocardiolipin acyltransferase 1 (termed ALCAT1), which is present in mitochondrial-associated ER membranes [50].

The phosphatidylserine decarboxylase (Psd1) of the inner membrane decarboxylates PS to produce PE (Fig. 3B) [51–53]. Psd1 represents the major source of cellular PE in the yeast cell [54]. Three alternative routes to produce PE exist in yeast. In the Kennedy pathway (CDP-ethanolamine pathway) PE is produced from free ethanolamine. Additionally, Psd2 in the endosome and the acyltransferases Tgl3 and Ale1 generate minor amounts of PE [55–57]. In mammals the Kennedy pathway is the major source of cellular PE [6,8]. All other phospholipids are synthesized in the ER. In yeast two PE methyltransferases (Cho2/Pem1 and Opi3/Pem2) catalyze the production of PC by a three-step methylation of PE [58–63]. Additionally, free choline can be converted to PC by the Kennedy pathway (CDP-choline pathway). Finally, PS and PI are synthesized by adding the headgroup serine or inositol to the activated lipid

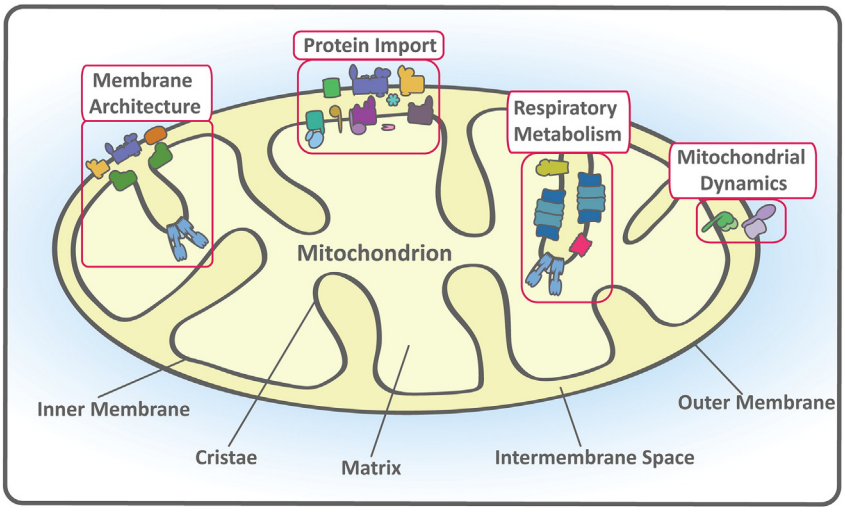

Fig. 1. Functions of lipids in mitochondria. Phospholipids form the hydrophobic core of the two surrounding membranes of mitochondria. They affect functions of protein machineries involved in respiratory metabolism, protein import, membrane architecture and mitochondrial dynamics. Additionally, phospholipids affect processes of mitophagy and apoptosis, which are not depicted here.

Please cite this article as: C.U. Mårtensson, et al., Effects of lipids on mitochondrial functions, Biochim. Biophys. Acta (2016), http://dx.doi.org/10.1016/j.bbalip.2016.06.015