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Review

Metabolism and function of mitochondrial cardiolipin

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ABSTRACT

Since it has been recognized that mitochondria are crucial not only for energy metabolism but also for other cellular functions, there has been a growing interest in cardiolipin, the specific phospholipid of mitochondrial membranes. Indeed, cardiolipin is a universal component of mitochondria in all eukaryotes. It has a unique dimeric structure comprised of two phosphatidic acid residues linked by a glycerol bridge, which gives rise to unique physicochemical properties. Cardiolipin plays an important role in the structural organization and the function of mitochondrial membranes. In this article, we review the literature on cardiolipin biology, focusing on the most important discoveries of the past decade. Specifically, we describe the formation, the migration, and the degradation of cardiolipin and we discuss how cardiolipin affects mitochondrial function. We also give an overview of the various phenotypes of cardiolipin deficiency in different organisms.

Contents

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1. Introduction

Cardiolipin (CL) is a unique phospholipid dimer consisting of two phosphatidyl residues linked by a glycerol bridge, i.e. 1',3'-bis(1,2-diacylglycero-3-phospho-)glycerol. CL occurs in various ATP-producing membranes of prokaryotes and eukaryotes, but we will limit this review to CL of mitochondria because lately, mitochondria have become a central aspect of research in cell biology. Along with the surging interest in mitochondria, there has been an explosion of papers addressing the role of CL. In a previous review on CL in this journal more than a decade ago, most if not all papers published on the subject were included [1]. Today, such an approach would be all but impractical. Instead, we decided to be selective and to include only those references that we felt are essential to the topics we wanted to discuss. As a result, we have omitted many papers, including many of our own, not to ignore them and certainly not to insult the authors but to focus on the key issues in this field that has become rather large. Furthermore, we have made an effort to cite mostly original articles rather than other reviews, except when the multitude and the convoluted nature of the original papers made it difficult to maintain an economic writing style.

2. The CL pathway of mitochondria

During the evolution of mitochondria, a large portion of their ancestral genome migrated into the nuclear compartment, which made mitochondria dependent on the import of proteins and lipids. However, mitochondria have maintained the ability to synthesize CL from its basic building blocks, glycerol-3-phosphate and fatty acids. The CL pathway can be divided into three parts, namely (i) the formation of phosphatidic acid (PA) and its translocation from the outer to the inner membrane, (ii) the conversion of PA to CL on the matrix side of the inner membrane, and (iii) the remodeling of CL, which in yeast takes place in membrane leaflets facing the intermembrane space (Fig. 1, Table 1). Thus, the overall process involves all mitochondrial compartments.

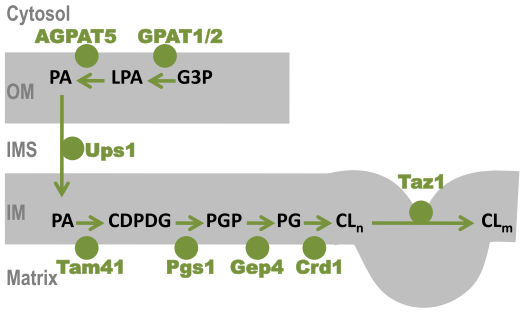

Fig. 1. Overview of CL biosynthesis in mitochondria. Glycero-3-phosphate (G3P) is acylated to lysophosphatidic acid (LPA) and then to phosphatidic acid (PA). PA formation occurs on the outer face of the outer mitochondrial membrane (OM) and in the endoplasmic reticulum. PA is transferred from the outer to the inner mitochondrial membrane (IM) via the intermembrane space (IMS) and is converted to CL on the matrix face of the IM via the intermedates CDP-diacylglycerol (CDPDG), phosphatidylglycerophosphate (PGP), and phosphatidylglycerol (PG). The final step of the pathway is the remodeling of nascent cardiolipin (CL_n) to mature cardiolipin (CL_m). Tafazzin, the remodeling enzyme requires disturbance of the bilayer packing order, such as high membrane curvature, in order to be active. In yeast, tafazzin faces the intermembrane space. Mammalian genes are shown for the enzymes of PA synthesis and yeast genes are shown for all other enzymes.

2.1. Supply of PA for CL formation

PA, the central precursor for the biosynthesis of neutral glycerolipids and glycerophospholipids, is formed by sequential acylation of glycerol-3-phosphate. In mammals, four proteins have been identified to carry glycerol-3-phosphate acyltransferase activity, two of which are localized in mitochondria (GPAT 1 and 2) and two of which in the endoplasmic reticulum (GPAT 3 and 4) [2]. The product of these enzymes is lyso-phosphatidic acid (LPA) that can be further acylated to PA. In mammalian mitochondria, acylation of LPA is catalyzed by AGPAT 5, a member of a large family of lysophospholipid acyltransferases [3]. The significance of having two branches of PA formation, one in mitochondria and one in the endoplasmic reticulum, has not been established. While the endoplasmic reticulum has traditionally been viewed as the principal site of lipid biosynthesis, mitochondrial glycerol-3-phosphate acylation has been associated with essential functions of its own, such as the synthesis of triglycerides [4] and mitochondrial fusion [5]. The frequently made assumption that it is the mitochondrial branch that supplies PA to the CL pathway has also not been proven. Mitochondrial PA is formed on the outer leaflet of the outer membrane [6], which is localized near the mitochondria-associated endoplasmic reticulum membranes. Thus, the two branches of PA formation are in close proximity to each other. Whatever the true source of PA is, it has to migrate across the outer membrane, the intermembrane space, and the inner membrane in order to reach the compartment where CL biosynthesis takes place. In yeast, Ups1 was identified as the lipid transfer protein that facilitates the transfer of PA across the intermembrane space [7].

2.2. Conversion of PA to CL

The biosynthesis of CL takes place on the matrix face of the inner mitochondrial membrane by a sequence of four reactions (Fig. 1). All enzymes have been unequivocally identified in yeast, a task that took until 2013 to complete (Table 1). Since most proteins of the inner membrane are arranged in various kinds of complexes, it seems likely that the four enzymes cluster around each other and are not scattered throughout the membrane. Localization of the pathway in the inner leaflet of the inner membrane has been demonstrated in liver mitochondria [8] but any more specific sub-compartmentalization, i.e. whether the enzymes are

Table 1
Enzymes of the mitochondrial CL pathway.

Step	Enzyme	Gene	References
G3P + acyl-CoA → LPA + CoA	Glycerophospate acyltransferase	GPAT1*, GPAT2*	[188,189]
LPA + acyl-CoA → PA + CoA	Acylglycerophosphate acyltransferase	AGPAT5*	[3]
PA transport	Lipid transfer protein	Ups1	[7]
PA + CTP → CDPDG + P ~ P	CDP-diacylglycerol synthase	Tam41	[10]
CDPDG + G3P → PGP + CMP	Phosphatiylglycerophosphate synthase	Pgs1	[14]
PGP + H_2O → PG + P	Phosphatidylglycerophosphate phosphatase	Gep4, PTPMT1*	[16,17]
PG + CDPDG → CL + CMP	Cardiolipin synthase	Crd1, CLS*	[18]
CL transacylation	Tafazzin	Taz1, TAZ*	[32]

The yeast nomenclature of the genes was used except for the ones marked by an asterisk.