Biochimie 95 (2013) 27–32

Contents lists available at SciVerse ScienceDirect

Biochimie

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

Mini-review

Implication of liver cardiolipins in mitochondrial energy metabolism disorder in cancer cachexia

Jean-François Dumas [a,b,*], Laure Peyta [a,b], Charles Couet [a,b,c], Stéphane Servais [a,b,d]

[a] INSERM UMR1069, "Nutrition, Growth and Cancer", F-37032 Tours, France
[b] Université François-Rabelais, F-37032 Tours, France
[c] CHRU Bretonneau, Tours F-37044, France
[d] IUT, Tours F-37082, France

ARTICLE INFO

Article history:
Received 27 March 2012
Accepted 10 July 2012
Available online 20 July 2012

Keywords:
ATP synthesis efficiency
Liver
Mitochondria
Nutrition
Undernutrition

ABSTRACT

Mitochondrial membranes are essential for the good functioning of the organelle. For instance, the inner mitochondrial membrane contains the oxidative phosphorylation system that permits ATP synthesis. Phospholipids environment and especially cardiolipin are crucial for the mitochondrial energy metabolism. Indeed, cardiolipin is known to provide essential structural and functional support to several proteins involved in oxidative phosphorylation. Alterations in cardiolipin structure, content and fatty acids composition have been associated with mitochondrial dysfunction in several physiopathological conditions and diseases. Cancer cachexia is a complex and dynamic process characterized by a negative energy balance induced by anorexia and hypermetabolism which leads to a drastic loss in body weight that aggravate prognosis of cancer patients. The underlying mechanisms of hypermetabolism are not fully understood. Whether the mitochondrial energy metabolism is altered during this disease and may participate to hypermetabolism is not clear. This mini-review focuses on cardiolipin especially its biosynthesis and remodeling pathways, its relation with mitochondrial energy metabolism and its possible implication in the cancer cachexia syndrome.

1. Introduction

Aerobic organisms synthesize ATP mainly by two ways, (1) glycolysis in the cytosol and (2) oxidative phosphorylation in the inner mitochondrial membrane in eucaryotes. Oxidative phosphorylation represents the major energy source, since it provides 17 times more ATP than glycolysis for the same quantity of degraded glucose. Inner mitochondrial membrane contains large amounts of proteins and lipids, most of which are composed of phospholipids (PL). Specific protein–lipid interactions occur that have been demonstrated essential for the structure, incorporation, and/or assembly of proteins or protein complexes and therefore for the good functioning of oxidative phosphorylation [1]. Among the phospholipids, cardiolipin (CL) is unique since it is specifically found in the mitochondrial membranes and it is a lipid dimer consisting of two phosphatidyl residues bridged by a glycerol and contains therefore four fatty acyl chains [2]. CL is intimately associated with all of the major players in oxidative phosphorylation and is therefore considered as a bioactive lipid in the inner mitochondrial membrane.

2. Mitochondrial energy metabolism

Mitochondria use oxidative phosphorylation to couple substrate oxidation and oxygen consumption to the production of ATP, the main form of useable energy that cells allocate toward cellular maintenance, proliferation, and work depending on physiological circumstances (Fig. 1). Mitochondrial respiration (oxygen consumption) consists in a serie of oxidoreduction reactions, from donors of electrons ($NADH^+ + H^+$ and $FADH_2$), coming from the degradation of metabolites (glucose, fatty acids, amino acids),

Abbreviations: acyl-CoA:lysocardiolipin acyltransferase, ALCAT; cardiolipin, CL; cardiolipin synthase, CLS; cytidine diphosphate, CDP; cytidine diphosphate diacylglycerol, CDP-DAG; cytidine monophosphate, CMP; cytidine triphosphate, CTP; diacylglycerol, DAG; endoplasmic reticulum, ER; fatty acids, FA; monolysocardiolipin, MLCL; monolysocardiolipin acyltransferase, MLCLAT; phosphatidic acid, PA; phosphatidylcholine, PC; phosphatidylethanolamine, PE; phosphatidylglycerol, PG; phosphatidylglycerol phosphate, PGP; calcium independent phospholipase A2, iPLA2γ; phospholipids, PL; protein tyrosine phosphatase localized to the mitochondrion-1, PTPMT-1; reactive oxygen species, ROS.

* Corresponding author. INSERM U1069, Laboratoire de Nutrition, Croissance et Cancer, Faculté de Médecine, Bâtiment Dutrochet, 10 boulevard Tonnellé, F-37032 Tours, Cedex 1, France. Tel.: +33 247 36 60 59; fax: +33 247 36 62 26.
E-mail address: jean-francois.dumas@univ-tours.fr (J.-F. Dumas).

0300-9084/$ – see front matter © 2012 Elsevier Masson SAS. All rights reserved.
http://dx.doi.org/10.1016/j.biochi.2012.07.009

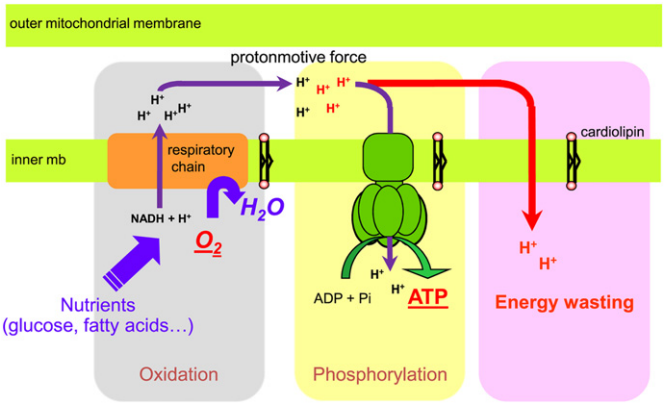

Fig. 1. Mitochondrial energy metabolism. Nutrients (glucose, fatty acids, amino acids) are oxidized into $NADH^+ + H^+$ and $FADH_2$. Reduced coenzymes are then re-oxidized toward a final acceptor (oxygen) by the mitochondrial respiratory chain. This transfer of electrons is accompanied by pumping of protons through the inner mitochondrial membrane toward intermembrane space. Electron energy is therefore stored in the form of an electrochemical gradient of protons or protonmotive force (Δp). The F_0–F_1 ATP synthase, uses the energy of the protonmotive force to couple the return of protons toward the mitochondrial matrix with the phosphorylation of ADP into ATP. At the whole this represents the oxidative phosphorylation and the oxygen consumption is therefore coupled to the ATP synthesis. However, oxidative phosphorylation is not a hundred percent efficient process, which means that not all the oxygen consumed by mitochondria (i.e. not all the substrate oxidized by the respiratory chain) is coupled to the mitochondrial production of ATP (energy wasting processes). CL plays an essential role in the optimal functioning of oxidative phosphorylation enzymes and also in the energy wasting processes.

toward a final acceptor that is oxygen. This transfer of electrons takes place within the respiratory chain and concerns 2 acceptors of electrons (ubiquinone and cytochrome *c*) and four enzyme complexes (complexes I, II, III and IV). Electron transfer is accompanied by pumping of protons through the inner mitochondrial membrane toward intermembrane space at complexes I, III and IV. Electron energy is therefore stored in the form of an electrochemical gradient of protons or protonmotive force (Δp). The protonmotive force is the sum of the membrane potential ($\Delta\Psi$) and of the pH gradient (ΔpH). A fourth proton pump, the F_0–F_1 ATP synthase, uses the energy of the protonmotive force to couple the return of protons toward the mitochondrial matrix with the phosphorylation of ADP into ATP. The inorganic phosphate (Pi), necessary for this reaction, is imported into mitochondria by the phosphate carrier. ATP formed is exported toward cytosol, in exchange of ADP, by the adenine nucleotide translocator (ANT). The all process represents the oxidative phosphorylation and allows the ATP synthesis from nutrients according to the chemiosmotic coupling theory [3]. In this coupled system, the maximum amount of ATP that mitochondria make per energetic substrate depends upon the efficiency of oxidative phosphorylation which is known as the ATP/O ratio. However, oxidative phosphorylation is not a hundred percent efficient process, which means that not all the oxygen consumed by mitochondria (i.e. not all the substrate oxidized by the respiratory chain) is coupled to the mitochondrial production of ATP (energy wasting processes). CL plays an essential role in the optimal functioning of oxidative phosphorylation enzymes such as ATP synthase and respiratory chain complexes and also in the energy wasting processes [4].

3. Cardiolipin

3.1. Structure and composition

CL is the common name used for diphosphatidyl glycerol or precisely 1,3-*bis*(*sn*-3′-phosphatidyl)-*sn*-glycerol. The name "cardiolipin" comes from heart tissue where this PL was first purified in 1942 [5]. In mammalian cells, CL is mainly located in the inner membrane of mitochondria, and accounts for 10–20% of total mitochondrial lipids. CL is also found in prokaryote organisms that use oxidative phosphorylation to fulfill their energy demand. CL is implied in oxidative phosphorylation as it is bound to different enzyme and acts on their activities. CL is a unique dimeric phospholipid in which two phosphatidic acids (PA) are linked by a central glycerol. Thus it contains four fatty acyl chains [5].

Although CL contains four fatty acyl chains the diversity of fatty acids (FA) composition is not as important as it could be. In fact, several studies have analyzed the FA composition of CL in different tissues and species. Data showed that the major species in rat heart, liver, kidney and skeletal muscle are 18:2 and 18:1 [6,7]. In bovine heart the main FA represented in CL are 18:2 and 18:3 [6]. In *Saccharomyces cerevisiae*, the main species are 18:1 and 16:1 [8]. The reasons for FA composition differences are not still completely elucidated, but can be attributed, in part, to CL metabolism and particularly to remodeling as the enzymes involved have FA specificities.

3.2. Cardiolipin biosynthesis and remodeling

The pathways of CL metabolism includes *de novo* biosynthesis and remodeling [2,9] (Fig. 2). CL biosynthesis pathway is similar to other PL biosynthesis since common intermediates such as PA and cytidine diphosphate-diacylglycerol (CDP-DAG) are involved [10]. However CL metabolism is unique because CL synthase (CLS) is a specific enzyme catalyzing the final step of *de novo* synthesis.

3.2.1. Biosynthesis

During the first step catalyzed by CDP-DAG synthase (CDS), a cytidine monophosphate (CMP) group from cytidine triphosphate (CTP) is linked to PA producing CDP-DAG. Then phosphatidylglycerol phosphate synthase (PGPS) catalyzes the formation of phosphatidylglycerol phosphate (PGP) from CDP-DAG by substituting CMP by glycerol phosphate group. Next, PGP is dephosphorylated into phosphatidylglycerol (PG) by PGP phosphatase identified in mammals as protein tyrosine phosphatase localized to the mitochodrion-1 (PTPMT-1) [11].

The final step is catalyzed by CLS which links PG to CDP-DAG with elimination of CMP group. This enzyme is the only one which is specific in this pathway and is found in the inner mitochondrial membrane with its catalytic site on the matrix side [6]. At this step CL are considered as immatures and will undergo an important maturation by FA composition remodeling.

3.2.2. Remodeling

CLS does not provide the final FA composition to CL since this is achieved by remodeling enzymes. CL remodeling is done in order to achieve FA composition specificity. Remodeling allows formation of mature CL and implies the following enzymes: a calcium independent phospholipase A2 (iPLA2γ), acyltransferases (monolysocardiolipin acyltransferase: MLCLAT and acyl-CoA:lysocardiolipin acyltransferase: ALCAT) and a transacylase (tafazzin) [2,9,12].

The initial step for remodeling is initiated by the deacylation of a single acyl chain by a phospholipase A resulting in monolysocardiolipin (MLCL) which is an intermediate. Gene CLD1 has been identified in yeast for encoding a mitochondrial protein with phospholipase A activity. This protein is a CL-specific deacylase with a substrate preference for palmitic acid [13]. In mammals, a study identified iPLA2γ with activity on CL in mice brain. However this enzyme seems not specific for CL as iPLA2γ is implied in deacylation of other PL such as phosphatidylethanolamine (PE) and phosphatidylcholine (PC) [14].