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Review

# Functional role of cardiolipin in mitochondrial bioenergetics ☆

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ABSTRACT

Cardiolipin is a unique phospholipid which is almost exclusively located in the inner mitochondrial membrane where it is biosynthesized. Considerable progress has recently been made in understanding the role of cardiolipin in mitochondrial function and bioenergetics. This phospholipid is associated with membranes designed to generate an electrochemical gradient that is used to produce ATP, such as bacterial plasma membranes and inner mitochondrial membrane. This ubiquitous and intimate association between cardiolipin and energy transducing membranes indicates an important role for cardiolipin in mitochondrial bioenergetic processes. Cardiolipin has been shown to interact with a number of proteins, including the respiratory chain complexes and substrate carrier proteins. Over the past decade, the significance of cardiolipin in the organization of components of the electron transport chain into higher order assemblies, termed respiratory supercomplexes, has been established. Moreover, cardiolipin is involved in different stages of the mitochondrial apoptotic process, as well as in mitochondrial membrane stability and dynamics. This review discusses the current understanding of the functional role that cardiolipin plays in several reactions and processes involved in mitochondrial bioenergetics. This article is part of a Special Issue entitled: Dynamic and ultrastructure of bioenergetic membranes and their components.


## 1. Introduction

Cardiolipin (CL) is commonly referred to as the signature phospholipid of the mitochondria. Among phospholipid species, CL has interesting chemical and structural characteristics, being highly acid and having a head group (glycerol) that is esterified to two phosphatidylglyceride backbone fragments rather than one, resulting in a very specific ultrastructure and role in the mitochondrial function. The diphosphatidylglycerol structure combined with four acyl chains gives cardiolipin its dimeric nature, which is unique among phospholipids and results in high specific conical structure. Cardiolipin is almost exclusively associated with membranes designed to produce ATP through the electrochemical gradient generated by the electron transport chain. Such membranes include the bacterial plasma membrane [1] and the inner mitochondrial membrane [2,3]. This ubiquitous and intimate association between CL and energy-transducing membranes suggests an important role for CL in mitochondrial bioenergetic processes.

Cardiolipin has been shown to interact with a number of inner mitochondrial membrane (IMM) proteins, enzymes and metabolite carriers [4–6]. The list of proteins that bind cardiolipin with high affinity is long and includes, among others, the electron transport chain complexes involved in oxidative phosphorylation (OXPHOS) and ADP/ATP carrier (AAC) (Fig. 1). Indeed, CL is required for optimal activity of complex I (NADH–ubiquinone oxidoreductase) [7–9], complex III (ubiquinone–cytochrome c oxidoreductase) [7,10,11], complex IV (cytochrome c oxidase) [12], and complex V (ATP synthase) [13]. Crystallographic studies have shown the presence of a few tightly bound CL molecules in each of the crystal structures of complex III [11], complex IV [14], and ADP/ATP carrier [15] as well as in crystallized prokaryotic proteins, such as the photoreaction center [16], the trimeric formate dehydrogenase-N [17] and succinate dehydrogenase [18]. These results suggest that CL is an integral component of these proteins, the presence of which is critical to folding.

Mitochondrial respiratory chain complexes assemble in higher order structure referred to generically as respiratory supercomplexes [19–21]. The unique, dimerically cross-linked phospholipid structure of CL seems to affect the stability and activity of such respiratory supercomplexes. Indeed, respiratory supercomplexes consisting of complexes III and IV are destabilized in mitochondria lacking CL [22–24]. Similarly, dimers of ADP/ATP carrier and other ADP/ATP carrier-containing complexes dissociated in CL-deficient mitochondria [22,25]. These examples illustrate the important role of CL for mitochondrial bioenergetic function; but in addition, recent studies are now revealing that CL has a much broader impact on mitochondrial physiology and pathophysiology [4–6].

Cardiolipin has been implicated in the process of apoptosis in animal cells through its interaction with a variety of death-inducing proteins, including cytochrome c (Cyt c) [26–29]. Cardiolipin-bound Cyt c acts

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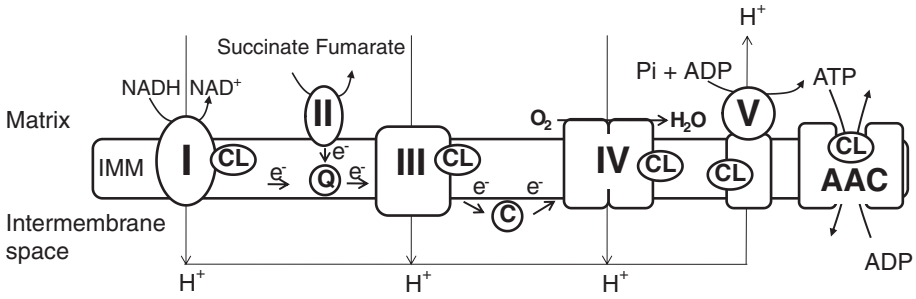


**Fig. 1.** Interaction of CL with oxidative phosphorylation complexes. The electrons are transferred along the path shown in the figure, resulting in the reduction of oxygen to water at complex IV. During this process, protons ($H^+$) are pumped by complexes I, III and IV into the intermembrane space to form an electrochemical gradient which is utilized by complex V to synthesize ATP from ADP and inorganic phosphate (Pi). ATP formed is then transferred by the ADP/ATP carrier (AAC) to the intermembrane space in exchange with ADP. Cardiolipin binds to complexes I, III, IV, and V and AAC. Q, coenzyme Q; C, cytochrome c; CL, cardiolipin.

as a peroxidase capable of catalyzing $H_2O_2$-dependent CL peroxidation, which is an essential step in the release of Cyt c during apoptosis [30]. Another function for CL in relation to energy metabolism is that it anchors two kinases, mitochondrial creatine kinase and nucleoside diphosphate kinase to the inner and possibly to outer mitochondrial membrane (OMM), where they come in contact [31,32].

Due to the role played by CL in mitochondrial bioenergetics as well as in apoptosis, it is conceivable that CL abnormalities may have important implications in mitochondrial dysfunction and hence, in cellular pathophysiology. Alterations in CL structure, content and acyl chain composition, associated with mitochondrial dysfunction, have been described in several pathophysiological conditions, such as hypo–hyperthyroid states [33–37], heart ischemia–reperfusion [38–42], nonalcoholic fatty liver disease [43], diabetes [44,45], Barth syndrome [46,47] and aging [48–51].

In this review, we discuss the current state of knowledge of the role played by CL in several reactions and processes involved in mitochondrial bioenergetics.

## 2. Cardiolipin and mitochondrial substrate carriers

The primary function of mitochondria is the synthesis of ATP by oxidative phosphorylation. In addition to this important role, these organelles are also the locus of other essential metabolic pathways, such as the citric acid cycle, fatty acid oxidation, the synthesis and degradation of amino acids (urea cycle), and the synthesis of iron–sulfur clusters and heme. To carry out these pathways, metabolites have to be continuously exchanged between the mitochondrial matrix and the cytoplasm. The inner membrane contains a mitochondrial carrier family (MCF) that catalyzes the transport of a number of metabolites between the intramembrane and matrix space [52]. Defined human diseases are now known to result from mutations in several members of this family [52]. One defining feature of the carriers is the so-called tripartite structure, consisting of three homologous sequence repeats of about 100 amino acid residues each, which was first noted in the sequence of the bovine ADP/ATP carrier [15].

Mitochondrial solute carriers constitute a major part of the inner membrane proteins. Several studies have shown that CL interacts with a number of mitochondrial carrier proteins and it is required for their optimal activity [53]. The mitochondrial phosphate carrier requires CL for its activity in proteoliposomes, and other phospholipids cannot substitute for CL [54]. In the heart, oxidation of pyruvate and β-oxidation of fatty acids are two major sources of ATP generation. The transport of pyruvate into the mitochondria by the pyruvate carrier and the exchange of carnitine esters by the carnitine: acylcarnitine translocase are critical for energy metabolism. The activities of both these translocases, reconstituted in proteoliposomes, have been shown to be most efficient in the presence of CL, and this could not be achieved by other phospholipids [55,56]. The tricarboxylate carrier has been demonstrated to be stimulated in the presence of CL, although the same stimulatory effect is observed in the presence of other phospholipids, such as phosphatidylserine and phosphatidylinositol [52]. Facing membrane lipids consisting of up to 20% CL, it is not surprising that mitochondrial carrier proteins interact with CL, this phospholipid being one of the major lipid components of the IMM. On solubilization of mitochondrial carriers, detergents replace to a large extent the membrane lipids. Without their native environment, the carriers become labile and the supplementation of phospholipids, especially of cardiolipin, may protect and facilitate the purification of the carrier in a functionally intact state. Preservation and stabilization of the native state of these carrier proteins by CL could explain the increased transport activity of these proteins, when measured in the reconstituted proteoliposomes. The importance of CL in maintaining the full catalytic activity of these carrier proteins may result from its unique large head group carrying two negative charges, requiring a specific and tightly interacting binding site, which may stabilize a protein domain in a clamp-like manner.

The ADP/ATP carrier plays an important role in energy metabolism by allowing the ATP formed by oxidative phosphorylation to pass across the IMM to intermembrane space. The movement of ATP is coupled by an antiport mechanism resulting in the 1:1 exchange of ATP for external ADP. Interestingly, the activity of the AAC has been shown to be optimal only in the presence of tetralinoleoyl–CL [53]. Other CL species, such as tetraoleoyl–CL and monolyso–CL, and also other phospholipids, were not effective in stimulating the AAC activity. There is also evidence from studies in yeast that absence of CL destabilizes the interaction of ACC with other mitochondrial proteins [25].

ADP/ATP carrier is the most abundant protein in the IMM (up to 10% of membrane proteins in bovine heart mitochondria), and this allowed for a detailed investigation of the carrier–CL interaction at molecular level. In fact, the availability of large amount of purified ACC protein and the strong stabilization of the structure by inhibitor ligand carboxyactractyloside (CAT), thus preventing protein unfolding and degradation [57], have allowed for the purification of the protein and its crystallization in the CAT-bound form. The crystal structure demonstrated that there are either two molecules of CL bound per monomer of ACC [15], or three molecules of CL bound per monomer of ACC [58]. The additional tightly bound CL found in the second crystal structure seems to be important in stabilizing protein–protein interactions in the crystal [15]. In addition to this X-ray structures, parallel $^{31}P$ NMR measurements have revealed the presence of tight bound CL to AAC [59]. The tight binding of CL can be rationalized in view of the large excess of positive charges in the AAC. A number of lysine residues have been suggested to face the lipid bilayer at the level of the membrane surface [53]. It was proposed that the CL molecules are bound at the lysine residues such that their headgroups face the matrix side. CL has the negative charges distributed over a large headgroup having two phosphates separated by glycerol. It is possible that the head group structure of CL allows it to bind optimally to sites on ACC. From the crystal structure

of ACC, both of the phosphate groups of each CL are involved through hydrogen bonding with main chain nitrogens and with carbonyls of symmetry-related residues, while the acyl chains of CL interacts with aromatic or hydrophobic residues. Interestingly, two CLs were localized at the interface of the adjacent ACC monomers involved in linking the monomers within a dimer. The phosphate groups are connected to the matrix short helices and two lysine residues of the opposing monomers. Thus, with the hydrophobic forces of the alkyl chains, CL seems to provide the glue for the dimer formation. It was proposed that the two CLs are also involved in the cross talk for the cooperative function of the monomers [58].

## 3. Cardiolipin and respiratory chain complexes

### 3.1. Cytochrome c oxidase

Cytochrome c oxidase (CcO) is a transmembrane protein–phospholipid complex that consists of 13 subunits with a combined molecular weight of 205 kDa. Of the 13 subunits of the mammalian CcO, the mitochondrial genome encodes subunits I, II and III, which form the catalytic core of the enzyme [60]. This enzyme complex spans the IMM and is in contact with 40–60 molecules of membrane phospholipids. Isolated detergent solubilized bovine CcO commonly contains 20–40 mol of phospholipids (phosphatidylcholine, phosphatidylethanolamine, cardiolipin) per mol of enzyme; however, only CL is known to be tightly bound with the isolated complex [12,61]. Cardiolipin is not a passive component of the CcO, but is functionally required for normal electron transport and proton translocation activity of this enzyme complex. Primarily based on purification and delipidation by chromatography and binding affinity assays [12,61], two classes of CL binding sites have been defined: two sites of high affinity and one to two additional sites with a lower affinity. The latter have been associated with structural integrity of CcO and of its dimeric form, because these CLs stabilize the subunit VIa and VIb, which are mandatory for the formation of the dimer. The two CLs binding CcO with high affinity are structurally and functionally important, and have been associated with the regulation of the electron activity of the enzyme. In fact, their removal from CcO destabilizes subunits interactions which are essential for full activity [12,62]. Removal of these CLs decreases electron-transport activity by around 50%; nearly full electron-transport activity is restored by the re-association of exogenous CL with CL-free CcO. Besides inducing activity loss, CL removal destabilizes CcO and specific subunits dissociate [62]. The crystal structure of bovine CcO homodimer has been determined to a resolution of 1.8 Å [63]. A combination of high resolution X-ray structure analysis of integral lipids in bovine CcO, with mass spectroscopy analysis of their chain lengths and the position of the unsaturated bonds of the hydrophobic tails, provides understanding of structural and functional roles played by these lipids in the CcO [64,65]. Thirteen lipids, including two CLs, one PC, three PSs, four phosphatidylglycerols and three triacylglycerols, were resolved in CcO. Crystallographic data resolves two unique CL binding sites on CcO. One CL is bound between subunit VIa on one monomer and subunit III on the other. The four acyl chains of CL interacts through van der Waals contacts with hydrophobic aminoacid residues belonging to both monomers, and two phosphate groups interacts with both monomers via hydrogen bond. Thus, the dimeric state of the bovine CcO is primarily stabilized by CL at subunit VIa. The second CL is located near subunit VIIa and stabilizes the association between this subunit with subunit I. A third CL (not resolved in crystal structure of bovine heart CcO) was found by photolabelling experiments with arylazido-containing CL analogs [64]. This CL is located between subunits VIIa and VIIc near to the entrance to the putative proton pumping channel, which contains a conserved aspartate. The authors hypothesized that this CL molecule could potentially function as proton antenna to facilitate proton entry into the channel, thus explaining the CL requirement for full enzymatic activity.

Very recently, the binding of CL to CcO in a monomeric form was explored by means of coarse-grain molecular dynamics (CGMD) simulation [66]. This technique has been successfully used to explore the lipid–protein interplay and more specifically lipid binding to variety of membrane proteins. The set of CGMD simulations obtained in this study, identified the precise positions of the CL binding sites on CcO. They agree with and reconcile all known experimental data. Most remarkably, two of the binding sites were found located at the matrix entrance of known proton uptake pathways (D and H) in CcO. In the context of the ability of CL to trap protons, these data support the notion that CL optimizes CcO electron transport activity by providing protons to the uptake pathway.

### 3.2. Ubiquinol cytochrome oxidoreductase

Complex III (ubiquinol-cytochrome c oxido-reductase), a multisubunit protein complex embedded in the IMM, is a central enzyme in oxidative phosphorylation which catalyzes electron transfer from membrane-localized ubiquinol to water-soluble cytochrome c. This redox reaction is coupled to the translocation of protons across the IMM. Bovine heart complex III is fully active after it is purified from mitochondria. The detergent-solubilized enzyme contains a number of bound CLs which are required for maintenance and stability of the functional and structural integrity of complex III [10]. Removal of these bound CLs by phospholipase A2 hydrolysis, destabilizes complex III resulting in an almost complete loss of activity and dissociation of subunits. Re-association of CL results in the stabilization of the quaternary structure of this enzyme complex and restoration of its full activity. This effect could not be replaced by other mitochondrial phospholipid species. This indicates that CL is either essential for catalytic function of complex III, or that it acts as an allosteric ligand that stabilizes the fully active conformation of this enzyme complex [10]. Several tightly bound phospholipids, including CL, were identified in X-ray structure of yeast complex III, while no bound CLs were detected in bovine or chicken heart mitochondria [11]. Destabilization of individual phospholipid-binding site in yeast complex III by site-directed mutagenesis, suggests that these phospholipids are important for structural and functional integrity of this membrane-associated protein complex, presumably stabilizing its dimeric structure. One CL molecule is found in a depression of cytochrome b, cytochrome c1 and Rieske protein closed to the site of ubiquinone reduction. This CL molecule appears to stabilize the architecture of the proton conduction environment at this site and may be involved in proton uptake [67]. Several mutations in this site either reduce electron transfer activity or reduce stability of associated subunits [68].

### 3.3. NADH CoQ oxidoreductase

Complex I (NADH-ubiquinone oxidoreductase) is a multisubunit integral membrane complex of the mitochondrial electron transport chain that catalyzes electron transfer from the NADH to ubiquinone. The redox reaction is coupled to proton translocation across the membrane, contributing to proton motive force. Mammalian complex I is a multi-subunit protein consisting of at least 45 dissimilar subunits with a total molecular mass of ~980 kDa [69,70]. Seven of the complex I subunits are mitochondrially-encoded and form the core of the enzyme; the remainder are nuclear encoded. The activity of this enzyme complex is considered the rate limiting step for mitochondrial respiratory chain and, therefore, an important factor in the regulation of OXPHOS process. Complex I is also considered an important site of superoxide anion generation in mitochondria [71–73]. Complex I seems to have a functional and structural requirement for bound phospholipids [7]. However, the structural and/or functional importance of phospholipids bound to complex I, especially CL, has not been conclusively demonstrated. Purified complex I usually has very low ubiquinone reductase activity unless it contains relatively high amounts of phospholipids, or the phospholipid depleted complex I is re-associated with a mixture of phospholipids that includes CL [7]. Recently, 9 CLs were identified in purified bovine

heart complex I in addition to 7 phosphatidylethanolamine (PE) and 12 phosphatidylcholine (PC) per complex [74].

Results from our laboratory have demonstrated that treatment of bovine heart submitochondrial particles with nonylacridine orange, a compound that interacts specifically with CL, resulted in a marked inactivation of complex I and that exogenous added CL fully prevented this inactivation, while other phospholipids such as PC and PE were ineffective [8]. In addition, decreased complex I activity in liver mitochondria isolated from rat fed with a choline-deficient diet, to model in animals' nonalcoholic fatty liver disease, could also be completely restored to the level of control liver by exogenous added CL [43]. Under condition of a choline-deficient diet, the mitochondrial content of CL decreased, due to the ROS-induced CL oxidation. Although no high-resolution crystal structure of the entire complex I is available, these findings strongly suggest the presence of functionally important CL molecules in the complex I.

### *3.4. Complex II (succinate dehydrogenase)*

Mitochondrial respiratory complex II is a tetrameric enzyme composed of a soluble catalytic heterodimer in the matrix and a heterodimer of membrane subunits in the IMM. Complex II serves as a link between the tricarboxylic acid cycle and the electron transport chain. This enzyme participates in oxidative phosphorylation but not in the proton-gradient during ATP synthesis. There appears to be no evidence for the association of CL to complex II. However, in a very recent study, Schwall et al. [75], using complex II enzymes reconstituted into nanoscale lipid bilayers (nanodiscs) with varying lipid composition, demonstrated, for the first time, that the phospholipid environment, specifically the presence of cardiolipin, is required for optimal stability, assembly and enzymatic activity of complex II, as well as curtailment of ROS production.

### *3.5. $F_0F_1$ ATP-synthase*

The mitochondrial $F_0F_1$ ATP-synthase (complex V) is a multisubunit complex which consists of two functional domains: $F_1$, situated in the mitochondrial matrix, and $F_0$, located in the inner mitochondrial membrane. Complex V uses the energy created by the proton electrochemical gradient to phosphorylate ADP to ATP. Complex V contains tightly bound CL, as demonstrated by characteristics $^{31}$P-NMR line broadening [59]. The CL:$F_0F_1$ stoichiometry in the delipidated complex V was 2.5:1. When phospholipids are removed from the $F_0F_1$ complex, its activity decreases to very low levels, while full restoration of this activity can be achieved by reconstitution with a variety of phospholipids. Observations made on the catalytic and structural characteristics of this enzyme complex, indicate that CL is able to influence properties of this enzyme more dramatically than the other major inner membrane phospholipids PC and PE [76].

$F_0F_1$ ATP synthase has been shown to form dimers [77] as well as higher oligomeric assemblies [78]. Proposed functional roles of oligomeric ATP synthase are stability advantages and an essential role for cristae formation [79]. Studies of the mitochondrial morphology of yeast mutants with destabilized ATP synthase dimers, confirmed the concept that dimeric and oligomeric arrangement of ATP synthase is involved in determining mitochondrial cristae morphology [80]. Very recently, Achean et al. [81] employed cryoelectron tomography to compare the structural organization of the complex V in flight-muscle mitochondria from wild-type, and CL-synthase mutant flies with virtually complete loss of CL. Their findings suggest that CL is critical for the degree of oligomerization and the degree of order in these ATP synthase assemblies, which is likely to affect cristae morphology and energy efficiency. It has been hypothesized that this effect of CL could either result from direct interaction with the enzyme, or from physical constraints associated with membrane curvature. Due to its molecular shape, CL is known to partition into high-curvature membrane segments and to adopt a specific orientation with respect to the intrinsic curvature, due to its inherent anisotropy. Thus, CL and ATP synthase might act in concert to reduce the free energy imposed by membrane curvature, together stabilizing these high-curvature folds [81].

## 4. Cardiolipin and mitochondrial supercomplexes

The mitochondrial electron transport chain (ETC) comprises four large protein complexes, which along with the $F_0F_1$ ATP synthase and mobile electron carriers (e.g. cytochrome c and coenzyme Q) constitute the machinery for converting metabolic energy into ATP. Since the consolidation of this view of the oxidative phosphorylation system, one contentious issue has been the nature of its physical organization. The currently favored view is the "random collision" model, first proposed by Hackenbrock et al. [82] (Fig. 2). According to this model, all components of the ETC are distinct entities that can diffuse individually in the mitochondrial membrane, and the electron transfer depends on the random transient encounter of the four individual protein of the complexes and the two small mobile electron carriers, CoQ and cytochrome c. ATP synthase is assumed to diffuse laterally in the membrane. In the solid-state model, first proposed by Chance and Williams [83], the enzyme components of ETC are assembled into a large supramolecular structure and the substrate is channeled directly from one enzyme to the next.

There is now a growing awareness that the individual components of the ETC assemble in higher order structure referred to generically as supercomplex or respirasome [19–21]. Evidence accumulated from functional and structural studies supports the existence of these supramolecular assemblies, which includes oxygen consumption characteristics [19] and metabolic flux analysis [84,85]. Several models of supercomplexes, involving components of the electron transport chain (complexes I, II, III and IV), and complex V and ACC carrier, have been proposed (Fig. 2). By using blue native electrophoresis after mild solubilization of mitochondria with digitonin, the existence of two supercomplexes composed by complexes I, III and IV with a stoichiometry of $I_1$, $III_2$, and $IV_4$, and by complexes III and IV with a stoichiometry of $III_2$ and $IV_4$, was demonstrated [19,86]. Such supercomplex organization of ETC would likely increase the efficiency of electron/proton

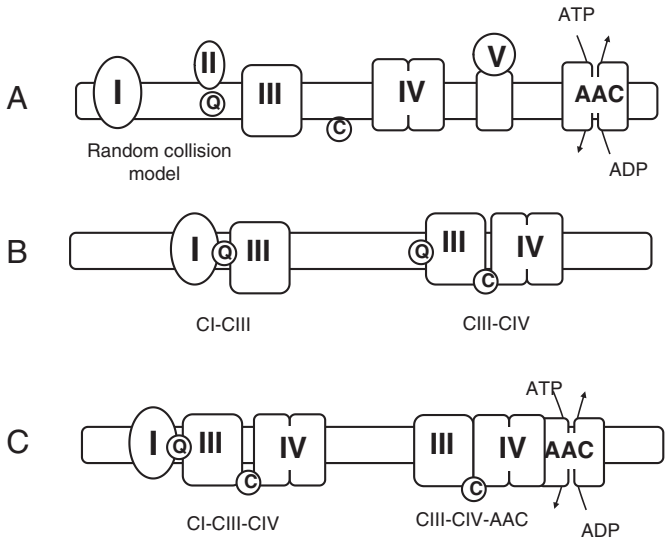


**Fig. 2.** Proposed models for the organization of oxidative phosphorylation complexes. Proposed models for the organization of ETC complexes (I, II, III, IV and V), and AAC into supercomplexes. Each complex in the supercomplex organization is shown as monomer. A, random collision model. B and C, supercomplex organization. For more details, see the text. Q, coenzyme Q; C, cytochrome c; AAC, ADP/ATP carrier.

flux and hence, that of ATP synthesis, while also minimizing the generation of potentially toxic reactive oxygen species, that have been proposed to be involved in the pathogenesis of cardiovascular and neurodegenerative diseases. This is consistent with the suggestion that the respirasome is a dynamic assembly, the aggregation states of which can respond to variations in the demand for energy under different physiopathological conditions [19].

Cardiolipin seems to participate in the structural organization and stabilization of the respiratory chain complexes in high order structure of functional importance [20,22–25,87]. Because these conclusions were drawn entirely from electrophoretic studies, it is important to note that a kinetic study of complex III/IV activity in isolated mitochondria also supports a role for CL in supercomplex formation [88]. Recent structural studies of the purified mammalian and yeast respiratory ETC supercomplexes by single particle cryoelectron microscopy [89,90] and cryoelectron tomography [91], resulted in three-dimensional density maps of atomic models for these structures, showing specific arrangements of individual complex in the supercomplexes. These studies revealed the presence of spaces between transmembrane domains of individual complexes which may by filled with phospholipids. About 200 CLs were estimated to be present in the purified bovine respirasome ($I_1III_2IV_1$), and about 50 CLs in the $III_2IV_2$ supercomplex from *Saccharomyces cerevisiae* [89]. This level of CL is in great excess over the amount of CL associated with the structure of the individual purified complexes (see above). The dependence on CL for supercomplex formation was clearly demonstrated in a recent study by Bazán et al. [92]. By employing a system composed of purified CIII and CIV from *S. cerevisiae* and liposomes of different phospholipid composition, these authors demonstrated, for the first time, the reconstitution of the supercomplexes $III_2IV_1$ and $III_2IV_2$ from individual CIII and CIV in proteoliposomes and specific dependence of CIII, CIV formation on liposomes containing CL in strong preference over other phospholipids. Thus, CL seems to be essential for supercomplex formation in addition to its occurrence as in integral part of individual complexes.

Recently, with a new dual-affinity tag, AAC was found to participate in the formation of these supercomplexes composed of one AAC dimer $(ACC)_2$ and two copies each of complexes III and IV [22]. In yeast mitochondria lacking CL, these complexes are absent or less defined, suggesting that CL is required for normal assembly and/or stability of the respiratory supercomplexes. Possibly, CL acts as a glue between these protein complexes by intercalating between the transmembrane sections of the components. The physical association of complexes III and IV in a supercomplex not only results in the enhanced efficiency of electron flow between these complexes, but also increases their proton-transporting capacity, thus creating a local microenvironment with relatively high electrochemical gradient. Moreover, CL has been suggested to function with the phosphate head groups as a proton trap, restricting pumped protons within its head-group domain, providing the structural basis for mitochondrial membrane potential ($\Delta\Psi$) and supplying protons for the ATP synthase [93]. Adjacent to the respiratory proton pumps, the buffering by CL would increase the voltage component $\Delta\Psi$ of the electrochemical gradient within the supercomplex. Therefore, in addition to connecting proteins and enhancing efficiency of electron flow, CL could locally contribute to creating a high $\Delta\Psi$ that is needed to drive the directional ATP export vs ADP import through the AAC across the mitochondrial membrane [53]. Through facilitating respiratory supercomplex assembly and recruiting AAC2, it has been suggested that under optimal conditions, CL increases the efficiency of OXPHOS by at least 35% [25].

The question arises how CL is incorporated into these protein complexes and which role CL plays in the overall process of complex assembly. The fact that many structurally unrelated proteins are able to engage in a strong binding with CL suggests that the structure of this phospholipid must provide a flexible force field that can adapt to a variety of protein surface. Further insight into the nature of CL–protein interactions may be derived from crystal structure. X-ray crystallography has been used to examine the structural details of an interaction between CL and the photoreaction center, a key light-driven electron transfer protein complex found in the *Rhodobacter sphaeroides*, where CL was for the first time resolved [16]. X-ray diffraction data showed that binding of CL to the protein involved a combination of strong hydrophilic interactions between the polar head group of CL with a number of aminoacid residues of the protein, involving electrostatic forces, hydrogen bonds and water molecules. Essential in these interactions is the ability of the phospholipid to fill cavities and grooves between hydrophobic interfaces of the protein located with the membrane bilayer, while providing specific ionic bridges at the water hydrophobic interface. Cardiolipin with unsaturated fatty acids is especially suited for this role with four twisted hydrocarbon domains and negatively charged hydrophilic domain [94].

## 5. Cardiolipin interaction with mitochondrial kinases

Another important role for CL in energy metabolism is to anchor two very large kinases, mitochondrial creatine kinase (mtCK) and nucleoside diphosphate kinase (NDPK) to the mitochondrial membranes [31,32]. Both mtCK and NDPK are located in the intermembrane/cristae space. In muscle and brain, creatine kinase provides a reserve supply of high energy phosphate (creatine phosphate) during initial signal period when the ATP is rapidly consumed. The evidence for the involvement of these two kinases in mitochondrial bioenergetics comes from the fact that they bind to voltage dependent anion channel (VDAC) and ATP/ADP exchange protein [32]. Both mtCK and NDPK fulfill two main functions, the functional coupling to inner membrane AAC and mitochondrial respiration, and the lipid transfer between membranes. A quantitative analysis of the properties of mtCK, in comparison with X-ray structure, shows the attachments with CL [95]. The structural basis and functional consequences of the CL interactions with mtCK and NDPK have been studied in detail and discussed in a recent review [96]. They mainly result in a functional interaction of mtCK and NDPK with the AAC, probably by forming proteolipid complexes in the IMM. These interactions allow for an exchange of metabolites, including ADP and ATP, between the mitochondrial matrix space and the cytosol, which ultimately regulates mitochondrial respiration. In addition, both mtCK and NDPK promote the transfer of lipids, including cardiolipin, between model membranes. This property may have important implications for apoptosis because it is known that cardiolipin moves from the inner to the outer mitochondrial membranes during apoptosis, and that this phospholipid provides a recognition site for Bcl2 proteins, notably t-Bid, to bind to mitochondria and promote the apoptotic process [96].

Interactions between components of the inner and the outer membrane are necessary for a number of central mitochondrial functions such as the channeling of metabolites, coordinated fusion and fission of mitochondria, and protein transport. Some of these interactions appear stable such as the so-called morphological contact sites. Both CL and PE appear to constitute the two major phospholipids present within the contact sites. A role for mtCK in the formation and stabilization of contact sites has been suggested. Epand et al. [96] described an interaction between the octameric ubiquitous form of mtCK and CL which potentially induced the lipid phase separation of CL into discrete domains in vitro. Within the contact sites, mtCK may bind to CL on the IMM and VDAC on the OMM to form a bridge across the bilayer of the mitochondria, which stabilizes the CL enriched contact sites. Thus, the interaction between CL and mtCK may have important implication for the apoptotic process.

## 6. Cardiolipin oxidation and ETC complexes

It is estimated that approximately 0.2–2% of the oxygen taken up by a cell is converted by mitochondria to ROS [97]. Within mitochondria, the electron transport chain is considered the main source of ROS. The primary ROS generated into the mitochondria is $O_2^{\bullet-}$, which is then

converted to hydrogen peroxide ($H_2O_2$) by spontaneous dismutation or by superoxide dismutase (SOD). Hydrogen peroxide, in turn, is broken down into water by glutathione peroxidase or catalase; if this does not occur, $H_2O_2$ can undergo Fenton's reaction in the presence of divalent cations such as iron to produce hydroxyl radical (•OH), which can be even more harmful to the mitochondrial biomolecules. The sites of superoxide anion production along the respiratory chain have been the subject of many studies [for a recent review see 98]. The two major sites of $O_2^{\bullet-}$ production are complex I and complex III. Mitochondria can produce superoxide anion, predominantly from complex I, when the matrix NADH/NAD+ ratio is high, leading to a reduced FMN site on complex I, and when they are not producing ATP and consequently have a high proton-motive force and a reduced coenzyme Q pool, leading to reverse electron transport. Based on inhibitor studies in heart mitochondria, the site of superoxide production at complex III is probably the unstable ubisemiquinone molecules [99] or cytochrome b [100]. It should be acknowledged that ROS are also produced to a lesser extent outside of the mitochondrion.

Cardiolipin molecules are particularly susceptible to ROS-induced oxidation, either for their fatty acyl composition or for their proximity to the ROS generating centers. In fact, CL molecules are rich in unsaturated fatty acids, particularly linoleic acid in heart and liver, or docosahexanoic and arachidonic acids in brain tissue mitochondria. In addition, CL molecules are located near to the site of ROS production, mainly represented by complex I and complex III of the respiratory chain. The presence of a methylene bridge between two double bonds of CL fatty acids renders these compounds sensitive to ROS-induced oxidation.

As mentioned above, CL molecules are required for functional activity of a number of inner mitochondrial membrane proteins, including respiratory chain complexes involved in OXPHOS. Thus, oxidative damage to CL may have deleterious effect on respiratory chain complex activity and mitochondrial function. Indeed, exposure of bovine heart submitochondrial particles to ROS generating enzymatic systems, resulted in a marked inactivation of complexes I, III, and IV, associated with a parallel oxidation/depletion of mitochondrial CL [8,101,102]. These alterations in ETC complex activity and in mitochondrial CL content were abolished by the addition of SOD + catalase. Interestingly, exogenously added CL-liposomes almost completely prevented the ROS-mediated loss in the activity of these respiratory chain complexes, while other phospholipids such as PE and PC and oxidized CL were unable to prevent this effect. Thus, the observed ROS-mediated defects in mitochondrial complex I, III and IV activity could be ascribed to ROS-induced CL oxidation/depletion. The exact mechanism by which CL oxidation affects the activities of these enzyme complexes is not well known. However, regarding CL oxidation-induced complex IV inactivation, destabilization of functional important subunit interactions and/or CL-hydroperoxide mediated peroxidation of key aminoacid residues, particularly tryptophans, has been suggested [103].

In addition to affect the activity of individual ETC complexes, ROS-induced CL oxidation may also affect OXPHOS supercomplex formation and/or stabilization. It was demonstrated by flux control analysis that the maintenance of a I–III supercomplex, after reconstitution of a protein fraction enriched with complex I and complex III into phospholipid vesicles at high protein to lipid ratios, is abolished if lipid peroxidation is induced by 2,2′-azobis-(2-amidinopropane) dihydrochloride (AAPH) before reconstitution [104]. Evidently, the distortion of the lipid bilayer induced by peroxidation and the alteration of the tightly bound phospholipids, determine the dissociation and destabilization of the supercomplex originally present in the lipid-poor preparation. Cardiolipin oxidation/depletion might have a primary role in this effect. Consistent with this, destabilization of mitochondrial respiratory chain supercomplexes, due to CL alterations, has been reported in Barth syndrome patients, and this may have important implications in the pathogenesis of this disease [105].

## 7. Cardiolipin and MPTP

Mitochondrial permeability transition pore (MPTP) is defined as the sudden increase of mitochondrial inner membrane permeability to low molecular weight solutes (1.5 kDa) in response to many stimuli, including high levels of $Ca^{2+}$ and oxidant stress. Opening of the MPTP by a combination of abnormally elevated intramitochondrial $Ca^{2+}$ and oxidative stress induces the collapse of transmembrane ion gradients, resulting in membrane depolarization and uncoupling of oxidative phosphorylation [106]. With reduced ATP levels, the cells cannot maintain structural and functional integrity, including ion homeostasis, resulting in irreversible damage and cell death, predominantly through necrosis. A number of molecules were accepted as key structural components of the MPTP, including, Cyp-D in the matrix, AAC and phosphate carriers in the inner membrane and VDAC (also known as porin) in the outer membrane [106–108]. Very recently, it was reported that reconstituted dimers of the $F_0F_1$ ATP synthase, incorporated into lipid bilayers, form $Ca^{2+}$-activated channels with properties identical to those of the mitochondrial megachannel, the electrophysiological equivalent of the MPTP [109], indicating dimers of the FoF1 synthase as a new putative component of the MPTP.

$Ca^{2+}$ ions are the most prominent inducers of the MPTP. Our studies have shown that exogenous added oxidized CL sensitized mitochondria to $Ca^{2+}$-induced MPTP opening [110]. Similarly, oxidation of endogenous CL by tert-butyl hydroperoxide, resulted in MPTP opening [111]. This synergistic effect of $Ca^{2+}$ and oxidized CL on MPTP opening suggests that both these compounds could play a coordinated role in this process by interacting with components of the MPTP, probably AAC. Cardiolipin molecules were shown to be tightly associated with AAC with a stoichiometry of three CLs per protein monomer [59]. It was also suggested that interaction between two monomers of the AAC is mediated by CLs, which could stabilize the dimeric structure by controlling the conformational changes, and participate in triggering a concerted ADP/ATP exchange [58]. Oxidized CL would destabilize the appropriate conformation of the AAC, favoring a conformation of this protein for MPTP opening. Bivalent cation $Ca^{2+}$ could be involved in this transition. Indeed, it was proposed by Brustovetsky and Klingenberg [112] that the bivalent cation $Ca^{2+}$, due to its high affinity for complexing CL, interferes with the interaction of AAC and CL, with a resultant structural change in AAC and its transition to a channel. It was also shown, in a study of AAC containing liposomes, that oxidized CL reversibly and competitively inhibits the activity of ANT [113]. Interestingly, the induction of MPTP opening by oxidized CL and $Ca^{2+}$ is associated with the release of cytochrome c from mitochondria [110]. The synergistic effect of $Ca^{2+}$ and oxidized CL in the induction of MPTP opening and in the release of cytochrome c from mitochondria (Fig. 3) may have important implications in cell death, as well as in those physiopathological situations characterized by alterations in $Ca^{2+}$ homeostasis and accumulation of oxidized CL in mitochondria, such as aging [48–50], heart ischemia/reperfusion [38,40,42,114] and other degenerative diseases. Thus, compounds able to prevent CL oxidation in mitochondria may open new perspectives for treatment of these disorders. There is continued interest in discovering new antioxidants or free radical scavengers of high potency and low toxicity that are effective in preventing CL oxidation in mitochondria. Among these compounds, melatonin [115] and plastoquinones [116,117] have been shown to be particularly effective in preventing CL oxidation in mitochondria by ROS attack. This would explain, at least in part, the protective effect afforded by these antioxidants against some pathophysiological situations and aging [118,119].

## 8. Interaction of cardiolipin with cytochrome c

Cytochrome c is a nuclear-encoded mitochondrial protein that is involved in life and death decisions of the cell. It participates in electron transfer of the ETC and it is, thus, an indispensable part of the energy production process. Cyt c also functions as a radical scavenger within

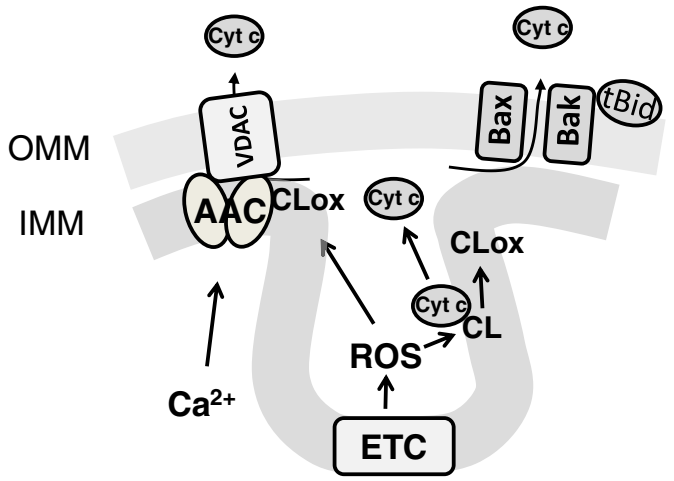


**Fig. 3.** Role of oxidized cardiolipin in the release of cytochrome c from mitochondria. ROS production causes cardiolipin oxidation which, in turn, promotes cytochrome c detachment from the IMM. Cytochrome c is then released into the cytosol through OMM, via MPTP or Bax/Bak oligomerization (for details see the text). OMM, outer mitochondrial membrane; IMM inner mitochondrial membrane; ETC, electron transport chain; AAC, ADP/ATP carrier; CL, cardiolipin; CLox, oxidized cardiolipin, Cyt c, cytochrome c.

the intermembrane space by removing unpaired electrons from superoxide, thus regenerating $O_2$ [120]. In addition, Cyt c plays a crucial role in the regulation of apoptotic process [28,29]. In fact, its release from mitochondria appears to be a central event in the induction of the apoptotic cascade that ultimately leads to programmed cell death.

Interactions between Cyt c and CL are an important determinant of apoptosis. Cytochrome c interacts with CL through two separate binding sites termed the A-site and C-site [28,121]. The A-site most likely involves weak electrostatic interactions between the phosphate groups of CL and lysine residues of Cyt c [122] and participates in the electron transfer and radical scavenging functions of Cyt c. The A-site is reversible and easily displaced by ATP or by increasing ionic strength. The C-site is a more stable interaction involving hydrophobic interactions and hydrogen bonding between one of the polyunsaturated acyl chains of CL and Asn52 residue of Cyt c. It has been suggested that one of the acyl chains of CL fits into a pocket of Cyt c, while the other three acyl chains remain in the membrane [121]. An alternative hypothesis suggests an interaction of two fatty acyls of CL with Cyt c [123]. The binding results in both partial unfolding and conformational changes of the Met-80 heme iron interaction, as well as spectral changes in the heme iron spin state [121,123]. The A-site interaction essentially tethers Cyt c to the membrane. Kagan et al. [30] found that CL bound cytochrome c acts as a peroxidase capable of catalyzing $H_2O_2$ dependent peroxidation and that CL oxidation is essential step in the release of cytochrome c during apoptosis. CL stimulates the peroxidase activity of cytochrome c by destabilizing the tertiary structure of this hemeprotein through the hydrophobic interaction, a process which is further enhanced by increases in the degree of CL unsaturation [124].

Besides to its role in promoting Cyt c release from mitochondria, CL modulates other steps of the apoptotic program. It has been demonstrated that CL in the OMM provides an anchor and activating platform for caspase-8, which is processed and translocates to mitochondria upon Fas receptor activation [125]. Activation of caspase-8 results in the cleavage of Bid (a BH-3 only protein) to a truncated form t-Bid which translocates to the OMM and induces the oligomerization of the proapoptotic proteins Bax and/or Bak (Fig. 3). Electron tomography studies showed that t-Bid interacts with mitochondria specifically at the inner and outer membrane contact sites, which are rich in CL [126]. Cardiolipin-rich membranes may adopt a non-bilayer hexagonal $H_{II}$ configuration at the contact sites, enabling access of CL to the cytosolic site of mitochondria. Moreover, the binding of t-Bid to mitochondria, by directly altering membrane curvature, may play critical roles in other apoptotic-associated processes such as cristae remodeling [127,128], and mitochondrial fragmentation [129]. Recruitment of t-Bid into a lipid microdomain of the OMM, most likely through CL binding, may be necessary for formation of multiprotein complexes which regulate changes in mitochondrial morphology.

Prior the release of cytochrome c from the mitochondria during apoptosis, a redistribution of CL occurs from the IMM to the OMM [130]. Here it participates in the formation of cytochrome c/CL peroxidase complexes and, after CL peroxidation, the formation of the MPTP which facilitates release of cytochrome c and other proapoptotic factors [110]. Thus, the depletion and remodeling of CL, the generation of ROS and CL peroxidase capability of cytochrome c, appear to play a coordinate role for an efficient release of cytochrome c from inner mitochondrial space [29,131].

## 9. Conclusions

Cardiolipin has pleiotropic roles in mitochondrial function. The exponential increase of articles on CL provide impressive evidence for the new interest in this subject. This review highlighted the role of CL in mitochondrial bioenergetics. Cardiolipin interacts with a number of proteins and enzymes involved in fundamental mitochondrial bioenergetic processes, such as respiratory chain complexes, mitochondrial substrate carriers and is required for their optimal activity. In addition, CL appears to play a role in the organization and stabilization of the OXPHOS complexes and AAC in supercomplexes, which may result in a more efficient electron/proton flux and hence, ATP synthesis. Thus, CL is crucial for mitochondrial oxidative phosphorylation and for correct function and structure of the IMM. How CL is incorporated into these protein complexes, how it modulates the activity of these proteins and which role CL plays in overall process of complex assembly, are questions for which a satisfying explanation has yet to be found. Elucidating the mechanism whereby CL mediates these activities remains an exciting area of future investigation. Cardiolipin is also emerging as an important player in the regulation of several of the mitochondrial steps in cell death and mitochondrial membrane stability and dynamics, including fusion and fission processes. Cardiolipin contains unsaturated fatty acyl chains which are readily oxidizable targets. Peroxidation of CL is now considered an important event in mitochondrial dysfunction in cellular pathophysiology and also an early step in apoptotic cell death. Abnormalities in CL content, fatty acyl chain composition and remodeling appear to be, at least in part, responsible for mitochondrial dysfunction associated with several pathophysiological situations, including hypo–hyperthyroid states, heart ischemia/reperfusion, heart failure, diabetes, Barth syndrome, as well as aging and age-related cardiovascular and neurodegenerative disorders. Pharmacological strategies designed to prevent CL oxidation may open new perspectives for treatment of these disorders.

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