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The role of mitochondrial cardiolipin in heart function and its implication in cardiac disease☆

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ABSTRACT

Mitochondria play an essential role in the energy metabolism of the heart. Many of the essential functions are associated with mitochondrial membranes and oxidative phosphorylation driven by the respiratory chain. Mitochondrial membranes are unique in the cell as they contain the phospholipid cardiolipin. The important role of cardiolipin in cardiovascular health is highlighted by several cardiac diseases, in which cardiolipin plays a fundamental role. Barth syndrome, Sengers syndrome, and Dilated cardiomyopathy with ataxia (DCMA) are genetic disorders, which affect cardiolipin biosynthesis. Other cardiovascular diseases including ischemia/reperfusion injury and heart failure are also associated with changes in the cardiolipin pool. Here, we summarize molecular functions of cardiolipin in mitochondrial biogenesis and morphology. We highlight the role of cardiolipin for the respiratory chain, metabolite carriers, and mitochondrial metabolism and describe links to apoptosis and mitochondria specific autophagy (mitophagy) with possible implications in cardiac disease.

1. Introduction

The failing heart has been considered as an "energy-starved engine that has run out of fuel" [1,2]. For an adult heart, the turnover of ATP per day has been estimated to be 6 kg. The heart converts chemical energy stored in fatty acids, lactate, and glucose into the mechanical energy to pump blood through the body. Mitochondria are key to this energy conversion as they provide 95% of this energy through oxidative phosphorylation. The Krebs cycle produces the reducing equivalents NADH and $FADH_2$, which are utilized by the respiratory chain and the F_1/F_o ATP synthase to generate adenosine triphosphate (ATP). High energy demand results in increased levels of ADP, which accelerates ATP production at the F_1Fo-ATP synthase and increases the activity of the respiratory chain. At the same time, production of reducing equivalents is increased by an upregulation of the Krebs cycle. Ca^{2+} plays a key role in activating several enzymes in the Krebs cycle. Ca^{2+} transmission from the cytosol into mitochondria is mediated by the mitochondrial calcium uniporter (MCU), which couples cytosolic elevation of Ca^{2+} induced by β-adrenergic stimuli with Ca^{2+} signaling in the mitochondrion. Besides their role in energy conversion, mitochondria have multiple functions in metabolism, such as the urea cycle, the metabolism of amino acids and lipids, and the biogenesis of heme and iron-sulfur clusters.

Many mitochondrial functions are strongly associated to mitochondrial membranes. The outer membrane (OM) plays a role in connecting the mitochondrion to different organelles in the cell, including the sarco- or endoplasmic reticulum (SR/ER), the lysosome, and the plasma membrane [3,4]. These contacts are important for interorganellar communication and allow for exchanging lipids and small solutes between organelles [5]. The inner mitochondrial (IM) separates two compartments, the intermembrane space (IMS) from the matrix compartment. Invaginations of the IM form cristae structures, which harbor the respiratory chain and are crucial for the energy conversion by oxidative phosphorylation. The IM also forms the inner boundary membrane where the IM is in close opposition to the OM, which are the sites of protein import from the cytosol. Mitochondrial membranes are characterized by a unique phospholipid pool containing the dimeric phospholipid cardiolipin (CL), which is specific to mitochondrial membranes. CL contains two phosphatidylglyceride backbone molecules and therefore binds four fatty acids. Different fatty acids bound to

Abbreviations: MAM, mitochondrial associated membrane; OM, outer membrane; IM, inner membrane; IMS, intermembrane space; CL, cardiolipin; PE, phosphatidylethanolamine; PS, phosphatidylserine; PA, phosphatidic acid

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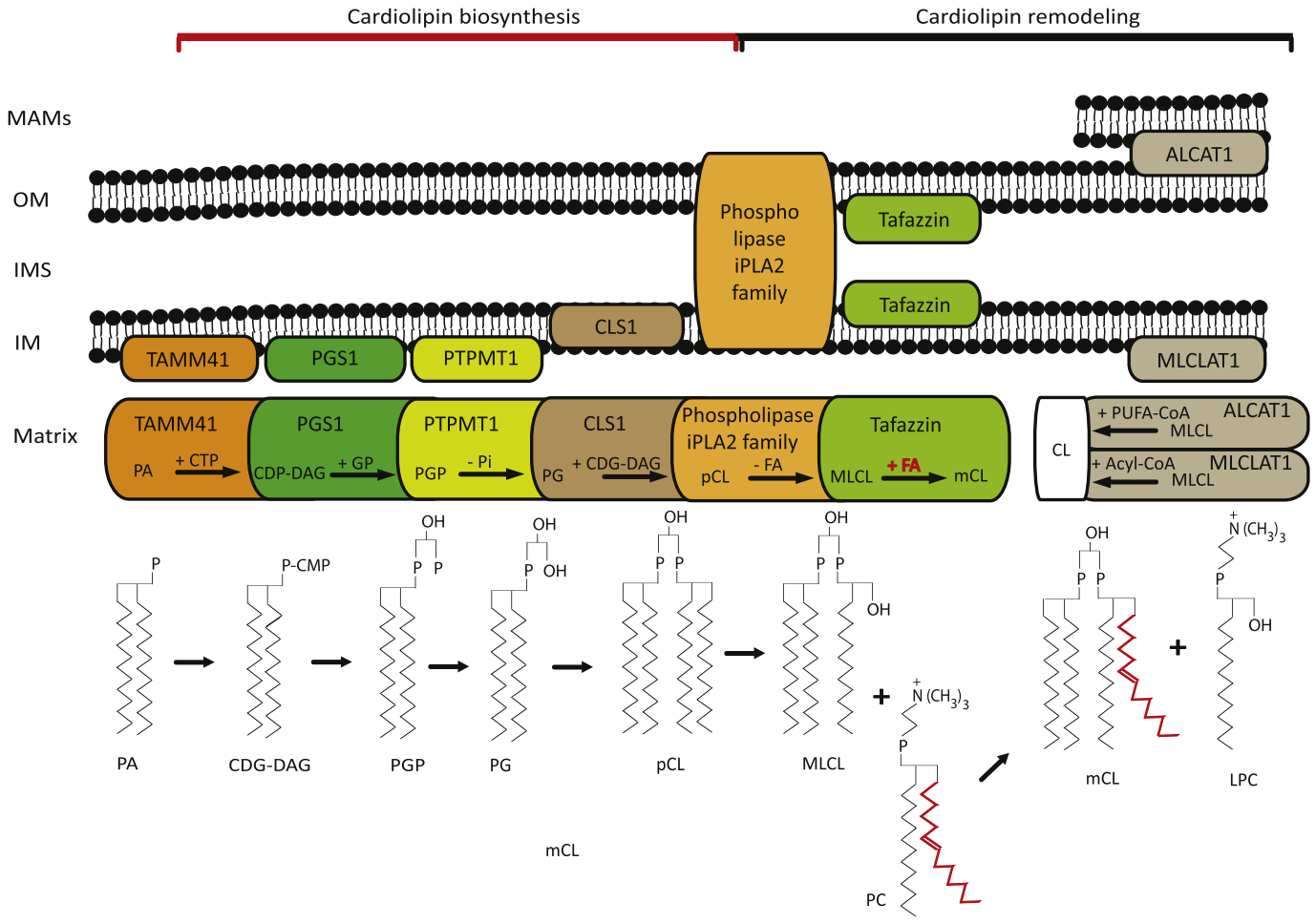

Fig. 1. Biosynthesis and remodeling of CL in mitochondria.
The biosynthesis pathway from phosphatidic acid (PA) to cardiolipin (CL) and enzymes involved are shown. After its initial biosynthesis, CL is remodeled through cleavage of one FA molecule by enzymes of the $iPLA_2$ family, which have not been defined yet. Subsequent, Coenzyme A independent reacylation is mediated by Tafazzin. The implication of ALCAT1 and MLCLAT1 in the acylation of MLCL is discussed in the text. The topology of the enzymes in the IM is shown. Tafazzin is associated to the IM and OM. OM, outer membrane; IM, inner membrane; IMS, intermembrane space; pCL, premature cardiolipin; CL, cardiolipin; PUFA, poly unsaturated fatty acid.

all four positions give rise to a highly diversified CL pool in most mammalian tissues [6]. In contrast, the mammalian heart has a very defined CL species composition, with linoleic acid (18:2) being the predominant form for all four acyl chains bound to CL [7]. CL is involved in many essential functions linked to mitochondrial membranes including mitochondrial morphology, mitochondrial metabolism, and respiration. Accordingly, defects in the biosynthesis and remodeling of CL have been linked with severe disorders such as Sengers disease and Barth syndrome. Here we provide an overview of CL biosynthesis and the role of CL in various aspects of mitochondrial biology. We discuss the impact of changes in CL amount and species composition on cardiac physiology in inherited cardiomyopathies and acquired diseases, such as ischemia/reperfusion injury.

2. CL biosynthesis, export and degradation

2.1. CL biosynthesis and remodeling

The reactions of CL biosynthesis are located in the inner mitochondrial membrane and originate from phosphatidic acid (PA) (Fig. 1). The initial reaction of PA with cytidine triphosphate (CTP) to cytidine diphosphate-diacylglycerole (CDP-DAG), is mediated by the CDP-DAG synthase TAMM41 [8]. The committed step in CL biosynthesis is catalyzed by the phosphatidylglycerol phosphate synthase (PGS1), which catalyzes the subsequent reaction of CDP-DAG and glycerol-phosphate to form phosphatidylglycerol phosphate [9–11]. PGS1 activity has been found to increase under conditions of mitochondrial biogenesis in yeast and is regulated by reversible phosphorylation [9,11]. The phosphatase PTPMT1 (Protein-tyrosine phosphatase mitochondrial 1) generates phosphatidylglycerol [12,13]. Phosphatidylglycerol reacts with a second molecule of CDP-DAG catalyzed by the Cardiolipin Synthase (CLS1) to form premature CL [14–16]. Thyroid hormones, which stimulate mitochondrial biogenesis were shown to regulate CLS1 activity [17]. An interesting study recently demonstrated induction of CL biosynthesis upon cold exposure in brown and beige adipose tissue in mice. Mice with a adipose tissue specific deficiency in CLS1 failed to adopt to cold exposure by heat production. CL biosynthesis was found to be required for enhanced mitochondrial respiration by activation of the uncoupling protein UCP1 [18]. Phosphatidylglycerol phosphate synthase (PGS1) and Cardiolipin Synthase (CLS1) are found to form a large oligomeric complex, which is tethered to the IM by binding to a scaffold of CL interacting proteins like prohibitin, stomatin-like protein 2 and the MICOS complex [19].

After its initial biosynthesis, CL is remodeled by exchange of fatty acids (Fig. 1). Mitochondrially localized members of the Ca^{2+} independent phospholipases ($iPLA_2$, $iPLA_2\gamma$, $iPLA_2$-*VIA*, and the 17β-hydroxysteroid dehydrogenase type 10 (HSD10)) have been suggested to catalyze the initial deacylation of CL to form monolysocardiolipin

(MLCL) [20–24]. Three enzymes have been proposed to catalyze the subsequent reacylation to form mature CL: MLCLAT1, ALCAT1 and Tafazzin. The coenzyme A-dependent monolysocardiolipin acyltransferase (MLCLAT1) was initially isolated from porcine mitochondria and described as a linoleoyl specific acyltransferase [25]. Expression of MLCLAT1 in Barth syndrome lymphoblasts increased CL levels [26]. The isolated enzyme shows high homology to the C-terminus of the α-subunit of the human trifunctional enzyme (α-TFP), involved in the β-oxidation cycle. As the N-terminal amino acids of α-TFP were absent in MLCLAT1, it was concluded that it is a splice variant of the HADHA gene encoding for α-TFP. Interestingly, also recombinant human α-TFP strongly interacts with CL [27] and α-TFP expression in Barth syndrome lymphoblasts elevated linoleoyl-CoA acylation of MLCL [28]. Lysocardiolipin acyltransferase (ALCAT1) is an ER-MAM resident enzyme catalyzing the coenzyme A-dependent reacetylation of CL [29]. Overexpression of ALCAT1 in mouse myoblasts increases the incorporation of docosahexaenoic acid (22:6) into CL, yielding a peroxidation prone form of CL. Since this form is also observed to increase in aging rat hearts, this modification might in fact reflect a pathogenic type of CL remodeling [30]. The third enzyme is Tafazzin, a protein that is highly conserved throughout species. Loss of Tafazzin function causes significant alterations in the cellular CL pool [31,32]. Tafazzin deficiency in BTHS patients causes a reduction in mature forms of CL and an increase MLCL [33]. The resulting increase in MLCL/CL ratio serves as a diagnostic marker for BTHS [34]. CL species shift to less saturated acyl side chains in Barth syndrome patients [35]. Due to these extensive remodeling in the CL pool, this coenzyme A-independent enzyme has been suggested to be the predominant enzyme in CL remodeling. Tafazzin catalyzes the reversible transacylation of one fatty acid molecule from lecithin (phosphatidylcholine) onto MLCL forming mature CL and lyso-lecithin. Interestingly, the substrate specificity of tafazzin is very low *in vitro* [36]. Recent data suggest that Tafazzin substrate specificity is determined by the physical properties of lipid domains in vicinity of the enzyme [37]. In this context it is important to note that the scaffolding proteins prohibitins (PHB) and the cochaperone DnaJ Heat Shock Protein Family Member C19 (DNAJC19) appear to form a dedicated lipid environment that is required for full activity of Tafazzin [38] (see Section 4.2). As a large number of different fatty acids can be bound to CL, a highly diversified CL species composition exists in different tissues. Therefore, loss of Tafazzin function in the BTHS mouse model causes tissue specific changes in the CL pool [39–41].

2.2. Lipid traffic: PA transport into mitochondria

The precursor for CL synthesis, phosphatidic acid (PA), originates from the membranes of the endoplasmatic reticulum (ER) and is transported into the mitochondria. Phospholipid traffic between ER and mitochondria is mediated by a tight interaction between both organelles, which has been termed Mitochondria Associated Membranes (MAM). Molecular tethers between both organelles have been identified recently. The dynamin related protein Mitofusin-2 is forming homo- or heterooligomeric complexes with Mitofusin-1, which are enriched in the ER-mitochondria interface [42]. How lipids are transported in between both organelles is poorly understood. The discovery of the endoplasmatic reticulum (ER)- mitochondria encouter structure (ERMES) in yeast and lipid binding domain in ERMES components has led to speculations of specific lipid binding proteins involved in the lipid transport between ER and mitochondria. The transport between mitochondrial membranes is mediated by a highly conserved family of PRELI (protein of relevant evolutionary and lymphoid interest) proteins in the intermembrane space, which are specialized in lipid transport (Fig. 2) [43,44]. PRELI domain-containing protein 1 (PRELID1; Ups1 in yeast) forms a complex with TP53-regulated inhibitor of apoptosis 1 (TRAIP1) (Mdm35 in yeast) in the IMS. Structural analyses in yeast have revealed the coordination of the PA molecule in a central hydrophobic cavity of the complex and basic residues interacting with negative charges of PA [45]. Dissociation of TRIAP1 from the complex at the target membrane is required for stable interaction of PRELID1 with the target membrane. The immediate conversion of PA into CL at the inner membrane ensures the directionality of the transport process [46]. Once a certain CL concentrations has been established in the inner membrane, PRELID1 (Ups1) does not dissociate from the target membrane and thus primes PRELID1 for degradation by the i-AAA protease, a mechanism suggested to regulate CL content in the IM. The PRELID1/TRAIP1-mediated transport does not account for the entire PA pool in mitochondria. The acylglycerol kinase (AGK) was recently discovered in the IMS and suggested to contribute to the PA pool by phosphorylating diacylglycerol (DAG) [47,48]. A second transport mechanism has recently been discovered in yeast. In a very similar way as described before for PA, the Ups2 homologues SLMO1 and SLMO2 associate in a complex with TRIAP1 in order to facilitate the transport of phospahtidylserine (PS) into the inner membrane (Fig. 2). PS is decarboxylated by PSD1 to form phosphatidylethanolamine (PE). PE synthesized in mitochondria, is required for mitochondrial morphology and respiratory function [49]. Interestingly, PS transfer is promoted by CL in the target membrane suggesting a reciprocal regulation of PE and PS by CL [50].

2.3. CL externalization upon mitochondrial stress

Despite the fact that CL biosynthesis takes place in the IM, CL was also detected in the OM [51,52]. Moreover, CL levels increase in the OM in response to cellular stress and apparently serves as a platform for the recruitment of specific signaling factors [53]. CL externalization has been observed after Rotenone mediated inhibition of respiratory chain complex I and with the kinase inhibitor staurosporine. Mitophagy is a process of specific removal of mitochondria by autophagy. CL on the OM plays a role in identifying dysfunctional mitochondria and specifically recruiting the autophagic machinery (Fig. 3) [53,54]. During apoptosis, for some pro-apoptotic factors, CL binding was shown to be required for efficient OM binding [55–57]. Thus, CL must be transported from the site of synthesis in the IM to the OM.

CL trafficking requires flipping CL molecules from the site of its biogenesis in the inner leaflet of the IM to the outer leaflet. As spontaneous phospholipid flipping in membranes is slow, this process requires acceleration by specific proteins. The phospholipid scramblase 3 (PLS3) is a lipid transporter in mitochondrial membranes, that can redistribute phospholipids. Knockdown of PLS3 prevents stress induced CL externalization, indicating a role of PLS3 in CL redistribution [53]. Two proteins in the IMS have been suggested to mediate the transport of CL from the IM to the OM: Mitochondrial creatine kinase (MtCK) is known for its role in the regeneration of phosphocreatine, which serves as an energy buffer to maintain cellular energy homeostasis [58]. The nucleoside diphosphate kinase (NDPK-D/NM23-H4) has a well-established function in maintaining the equilibrium between di- and triphosphate nucleotides. Both, mtCK and NDPK have been found to interact with CL and therefore have been suggested to mediate CL transfer between the inner and outer membrane. Both proteins form large oligomeric complexes in the intermembrane space, which were suggested to physically assist to connect IM and OM [59–61]. Interestingly, mtCK requires CL not only for membrane binding but also for full kinase activation [62].

2.4. CL degradation

Compared to the turnover of other mitochondrial phospholipids, the turnover of CL is relatively slow [63]. CL stability is explained by the extensive interaction of a large CL pool with membrane protein complexes including the respiratory chain [64]. When this association is lost as is the case in Barth syndrome (see Section 4.1), CL may become more susceptible to degradation. The involvement of enzymes of the phospholipase A family in the turnover of CL has been suggested. The

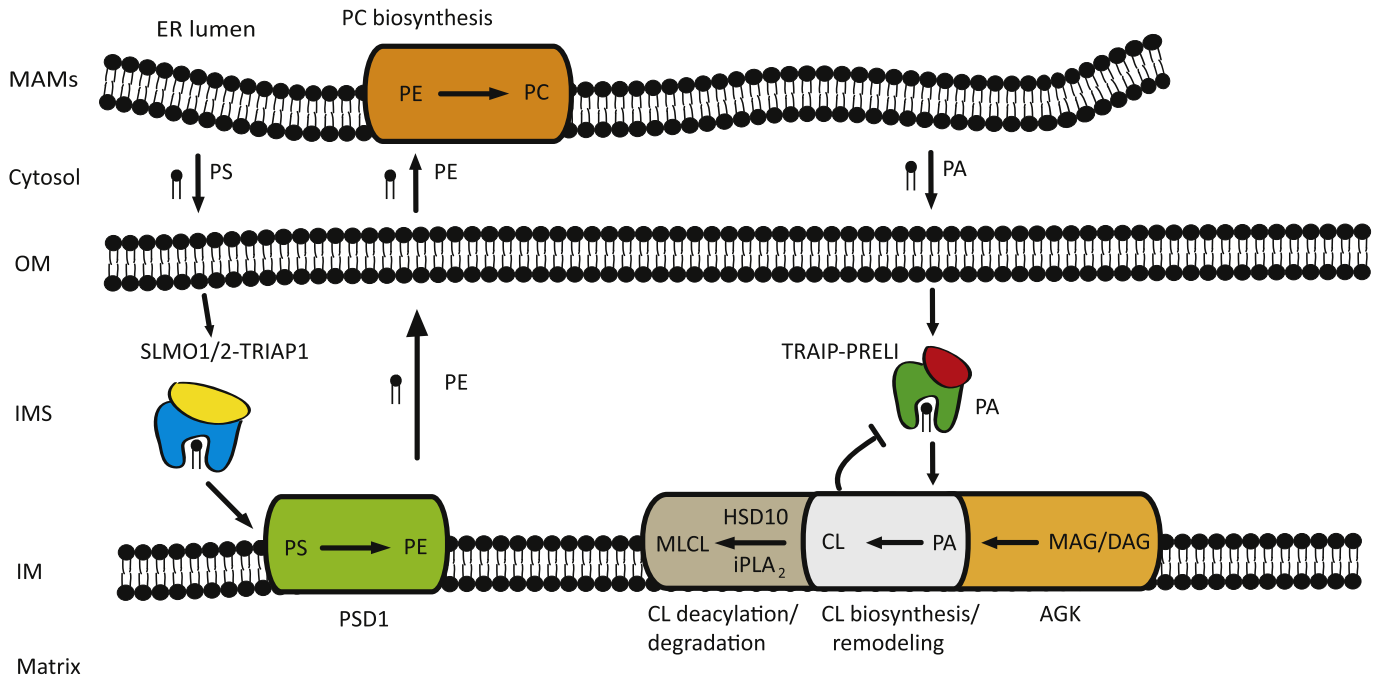

Fig. 2. Phospholipid transport into mitochondria relevant for CL biosynthesis.
Transport of phosphatidic acid (PA) into the inner mitochondrial membrane is mediated by TRAIP1 forming a complex with PRELID1. Phosphatidylserine (PS) is transported to the IM for its conversion to phosphatidylethanolamine (PE) with the help of the SLMO 1/2-TRIAP1 complex. In a negative feedback loop CL inhibits transport of PA but promotes transport of PS into mitochondria. The acylglycerol kinase (AGK) forms CL from diacylglycerol (DAG). MAM, mitochondrial associated membrane; OM, outer membrane; IM, inner membrane; IMS, intermembrane space.

cytosolic PLA_2 ($cPLA_2$) hydrolyzes monolyso- and dilyso-CL but not CL [65]. The splice variant, $cPLA_2\beta3$, is localized in mitochondria however a role for CL degradation has not been investigated [66]. CL is strongly susceptible to oxidation, which is deleterious for mitochondrial function. The phospholipase HSD10 has been suggested to mediate the rapid degradation of oxidized CL [24]. Therefore, HSD10-mediated CL clearance might be required for the maintenance of functional mitochondria. Human phospholipase D, (MitoPLD), has been shown to hydrolyze CL to form PA in the outer mitochondrial membrane [67]. PA has several functions in maintaining mitochondrial morphology (see Section 3.2). However, a role of MitoPLD in CL homeostasis has not been investigated.

3. Functions of CL in mitochondria

3.1. Links between lipid homeostasis and protein import into mitochondria

The mitochondrial proteome contains about 1500 proteins [68,69] which are mostly nuclear encoded and are directed into mitochondria by specific mitochondrial targeting signals [70,71]. Membrane-embedded mitochondrial protein translocases import proteins from the cytosol and direct them to their final destination in IM, OM, IMS or the matrix. The first translocation step across outer membrane is, with a few exceptions, mediated by the translocase of outer membrane (TOM) [72]. After crossing the outer membrane, proteins are targeted to their final destination in the outer membrane, the inner membrane, matrix or intermembrane space (Fig. 3). For many protein translocases, including TOM, a structural dependence on CL has been documented [52]. β-barrel proteins constitute a large protein family in the outer membrane and require the Sorting and Assembly Machinery (SAM) for their integration into the outer membrane. Since the assembly of the SAM complex is CL dependent, the integration of β-barrel proteins into the OM is strongly affected in CL deficient cells [52]. Moreover, CL plays a role in transport of carrier proteins into the inner membrane. Carrier proteins are a large family of proteins, which mediate the transport of metabolites across the inner membrane. They are characterized by a uniform organization of six alpha helical transmembrane spans. The family of carrier proteins is integrated into the inner membrane with the help of the TIM22 complex, which requires CL for its structural integrity [8,73,74]. Interestingly, the acylglycerol kinase (AGK), involved in the biosynthesis of phosphatidic acid (PA), was shown to also be a structural component of the TIM22 complex [48,75]. However, the function of AGK in protein translocation is independent of its kinase activity. Accordingly, AGK appears to have dual function in mitochondria and impairment of both may contribute to Sengers syndrome (see Section 4.3).

Proteins, which are targeted to the matrix or the inner membrane are transported by the presequence translocase (TIM23 complex). The membrane-embedded TIM23 complex associates to the translocase associated motor complex (PAM), which drives the ATP-dependent import of precursor proteins. The integrity of the TIM23 complex and its association with PAM depend on CL [8,74,76]. Recently, CL was found to be required for the association of the TIM23 complex with its receptor protein Tim50 [77]. After import and maturation mitochondrial proteins fold and integrate cofactors. Data from yeast suggest that also cofactor integration, such as iron sulfur clusters, is a CL dependent process [78]. Thus, assembly and transport processes in mitochondria are heavily dependent on CL in the corresponding membranes.

3.2. A role for CL in mitochondrial morphology

Mitochondria are highly dynamic organelles, which form an interconnected network. In the heart, the mitochondrial network forms multiple interactions with other organelles including ER [79], lysosomes [4,80] and the plasma membrane [81]. Molecular tethers connecting ER and mitochondria, ensure a regular distance of 10–25 nm [82]. The tight interaction between both organelles is thought to facilitate lipid exchange between the organelles (see Section 2.2).

In yeast, the ER-mitochondria encounter structure (ERMES) complex mediates a physical connection between ER and OM. ERMES

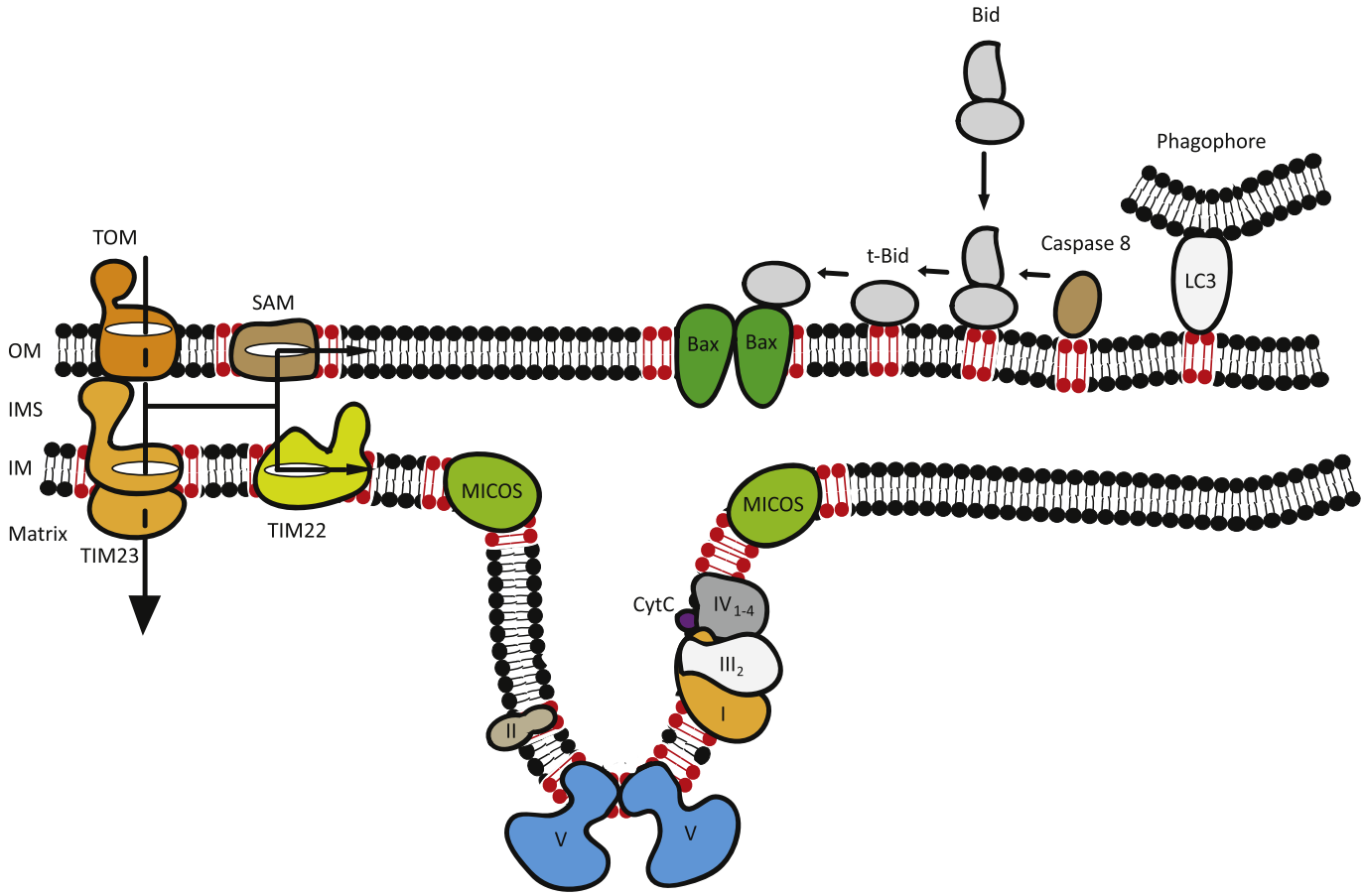

Fig. 3. The role of CL in mitochondrial metabolism and as a signaling platform.
CL is required for the structural integrity of protein translocases and the MICOS complex. It also plays an important role for the structure of respiratory chain complexes and the assembly into respirasomes. Upon mitochondrial stress CL is externalized and serves as a binding platform for the recruitment of LC3, mediating mitophagy, or caspase-8, Bax and Bid mediating apoptosis. OM, outer membrane; IM, inner membrane; IMS, intermembrane space.

components contain TULIP (tubular lipid binding) domains and a role in lipid transport has been suggested. In mammals, the dynamin-related protein Mitofusin-2 (Mfn2), locates in the ER/SR membrane and in the OM. By forming homo- or heterooligomeric complexes with Mitofusin-1 (Mfn1), on the OM [42], it contributes to a tight interaction of both organelles [83]. Protein complexes also shape the morphology of the inner mitochondrial membrane. Essential for the formation of the characteristic cristae structures is the conserved Mitochondrial contact site and cristae organizing system (MICOS) complex residing in the inner membrane at the cristae junctions (Fig. 3) [84]. One MICOS constituent directly interacts with CL and a role in forming local CL pools in membrane areas of high membrane tension has been suggested [85,86]. As the MICOS complex functionally interacts with multiple components in the OM, it has been proposed to be central to an interaction network linking IM, OM, ER membrane and adjacent aqueous compartments (ERMIONE, ER–mitochondria organizing network) [87].

The mitochondrial network morphology is maintained by a dynamic equilibrium of fusion and fission. Both processes are mediated by dynamin like GTPases in the inner and outer membrane. Fission is mediated by the recruitment of the cytosolic GTPase Dynamin-1-like protein (Drp1) to the OM. Drp1 oligomerization into helical structures constricts the OM and is required for separation of two mitochondria [88]. CL binding to DRP1 enhances oligomerization and GTP hydrolysis, indicating a role of CL for regulating mitochondrial fission [89,90]. Mfn1 and Mfn2 in the OM and Dynamin-like 120 kDa protein (Opa1) in the IM are necessary components of the fusion machinery [91]. CL might be involved in defining local regions of membrane fusion and fission. The phospholipase MitoPLD in the OM converts CL to phosphatidic acid (PA). PA was shown to promote mitofusin-mediated fusion of the outer membrane [92]. Subsequent turnover of PA by the phospholipase PA-PLA$_1$ or the phosphatase Lipin 1b opposes this effect [67,93]. The dynamin-related GTPase Opa1 mediates fusion of the IM after two mitochondria have fused their OM. The full-length forms of Opa1 are integrated in the IM, exposing their GTPase domain into the IMS. Alternative splicing and proteolytic processing give rise to long and short forms of Opa1 and both forms assemble into dimeric complexes. Imbalanced Opa1 processing in cardiac tissue can cause metabolic remodeling of the heart resulting in dilated cardiomyopathy [94]. CL binding is required for the dimerization and induction of the GTPase activity [95,96]. In addition, a novel mechanism for coordinating inner and outer membrane fusion was proposed, in which CL binding to the IMS domain of Opa1 allows a direct contact with the IM of the target mitochondrion [97].

Defects in the mitochondrial CL pool are associated with diseases like Barth syndrome (BTHS) or Sengers disease (DCMA). Characteristic for both diseases are significant changes in mitochondrial morphology. Analysis of lymphoblasts from healthy individuals and BTHS patients by electron tomography revealed a more heterogenous size distribution with higher numbers of smaller and larger mitochondria in BTHS. Cristae structures were strongly reduced and the regular arrangement of the inner membrane in cristae structures was strongly affected in BTHS [98]. An emerging concept that morphological alterations of mitochondria have a direct role in detrimental changes in the metabolism is currently under investigation [99,100].

3.3. Cardiolipin in OXPHOS complexes and respirasome formation

Five complexes (complex I-V) in the inner mitochondrial membrane form the oxidative phosphorylation system. The reducing equivalents, NADH and $FADH_2$, are transferred onto complex I and complex II of the respiratory chain, respectively. Electrons are transferred to ubiquinone and then *via* complex III to cytochrome *c*. The cytochrome *c* oxidase (complex IV) transfers electrons onto the terminal electron acceptor molecular oxygen. The electron transfer is coupled with a proton export across the membrane by complex I, III and IV. The resulting membrane potential allows complex V to store the energy within the chemical bonds of adenosine triphosphate (ATP). The largest complex of the respiratory chain is complex I, which consists of 45 subunits (Fig. 3). It is functionally the first complex and transfers electrons from NADH onto ubiquinone. Structural analyses revealed specific interaction sites for CL and a requirement of CL for full activity of complex I [101,102]. Complex II consists of four subunits and transfers electrons derived from the oxidation of succinate onto ubiquinone. Reconstitution of complex II into Nano Discs required CL for complex II stability and optimal enzymatic activity [103]. A reduction of complex II subunits was observed in cells with a defect in Tafazzin mediated CL remodeling [39]. The transfer of electrons from ubiquinone to cytochrome *c* is mediated by complex III, which is a dimeric complex with 11 subunits per monomer. The isolated complex contains several CL molecules. One CL binding site locates at the interaction site of the complex III dimer [104]. A second site is located near the ubiquinone reduction site (Q_i) implying a role for CL in H^+ pumping activity [105]. The cytochrome *c* oxidase (Complex IV) consists of 13 subunits, three of which represent mitochondrial-encoded proteins (COX1–COX3) forming the catalytic core. Complex IV contains high affinity and low affinity binding sites for CL. CL binding was found to be necessary for the structural integrity of complex IV. As CL binding site resides in close proximity to the entrance to the putative proton pumping channel, it may also be directly involved in proton transport [106,107]. Complex V uses the energy stored in the proton gradient across the inner membrane for the synthesis of ATP. Complex V binds CL and CL is required for its full activity [108,109]. A direct mechanistic role of CL in the proton translocation at complex V has also been suggested [110]. Moreover, CL is critical for the degree of oligomerization of complex V, which is affects bending of mitochondrial inner membrane in the cristae.

Another organizational level of respiratory chain complexes is the formation of large oligomeric structures, so called supercomplexes formed by complex I, III and IV [111–114]. Cryo-electron microscopy provided structural insight of the respiratory chain supercomplexes. In these structures, the large membrane arm of complex I forms a cavity for interactions with the dimer of complex III. Complex IV resides at the outer end of this membrane arm forming interactions with complex I and III [115–118]. Supercomplex formation likely increases efficiency the electron/proton flux and minimizes the generation of toxic reactive oxygen species (ROS). CL molecules were found to be directly associated with the respiratory chain supercomplex [119,120]. It is speculated that CL resides in spaces between the membrane domains and supports the supercomplex structure. Indeed, a loss of respiratory chain supercomplexes was found in CL deficient cells [121–126]. A second function as proton trap has also been described for CL: as the uptake of one proton is stabilized by a resonance structure, CL provides a molecular support for the membrane potential [127]. While CL supports respirasome assembly, the phospholipid phosphatidylethanolamine appears to counteract CL and destabilizes respiratory chain supercomplexes [128]. Thus, a balance of phospholipids is required to maintain functional respirasomes.

Metabolites, destined for the mitochondrial matrix, have to cross two membranes. In the outer membrane the β-barrel protein Voltage-dependent anion-selective channel protein 1 (VDAC) allows transport of a large number of molecules up to a size of 5 kDa. The inner membrane must be tight to prevent uncontrolled proton leakage. Hence, specific metabolite carriers mediate the transport of the large number of different substrates across the inner membrane. The superfamily of carrier proteins is characterized by six transmembrane domains [129]. CL has been found to be tightly associated with the ADP/ATP carrier (ANT) [130] and was in fact identified in the crystal structure of ANT from bovine heart mitochondria [131]. CL molecules are also localized at the interface of two monomers, providing a potential link for dimer formation [132]. In yeast, ANT has been shown to interact with respiratory chain supercomplexes and this association is dependent on CL [133]. A requirement for CL has also been documented for other members of the carrier family including the Phosphate carrier (PiC) [134] the monocarboxylate carrier (MCT1) [135], Carnitine/acylcarnitine translocase [136], pyruvate carrier [137] and the tricarboxylate carrier [138]. These analyses show that the inner membrane lipid composition impacts assembly and transport processes required for metabolite exchange with the cytosol.

3.4. Role of cardiolipin in metabolic functions

Many mitochondrial enzymatic activities are associated with mitochondrial membranes and require CL for full activity. Here we provide a short overview of mitochondrial functions for which CL requirement has been established.

Biosynthesis of steroid hormones occurs to a large part in the endoplasmatic reticulum. However, the first step takes place at the inner mitochondrial membrane and is catalyzed by cytochrome $P\text{-}450_{SCC}$. Cytochrome $P\text{-}450_{SCC}$ (*CYP11A1*) resides in the matrix side bound to the inner mitochondrial membrane. It catalyzes the committed step of steroid hormone synthesis by cleaving the side chain of cholesterol to form pregnenolone. CL binds to $P\text{-}450_{SCC}$ and is a potent activator of its enzymatic activity [139].

Reducing equivalents (NADH) produced in the cytosol are unable to cross the inner membrane to deliver electrons to the respiratory chain. Two isoforms of the glycerol-3-phosphate dehydrogenases (GPDH) in cytosol and mitochondria allow transfer of cytosolic reducing equivalents to the mitochondrial respiratory chain. Dihydroxyacetone phosphate reduced to glycerol-3-phosphate by the cytosolic GPDH mediates electron transfer to mitochondrial form of GPDH. Mitochondrial GPDH in the inner mitochondrial membrane catalyzed the reverse reaction and transfers electrons onto the mitochondrial ubiquinone pool. CL has been reported to bind to mitochondrial GPDH and is required for the activity of this enzyme [140].

3.5. Role of CL in mitophagy and apoptosis

Autophagy allows the degradation of damaged or superfluous organelles by the lysosome. Mitophagy is a form of autophagy, selective for mitochondria. Damaged mitochondria are enclosed by a double membrane structure, the phagophore. The autophagosome then fuses with the lysosome releasing its content for degradation [54]. Mitophagy is not only essential during cardiac development but also maintains cardiac function in the adult heart [141–144]. Upon induction of mitophagy the content of CL in the OM is increased [53]. This finding has led to the general concept of CL externalization during mitochondrial stress (see Section 2.3). CL exposed to the OM forms a signaling platform for the recruitment of essential adaptor molecules connecting the autophagic machinery specifically to damaged mitochondria. Externalized CL is recognized by Beclin 1, which is a central regulator in the early stage of phagophore formation [145]. Beclin 1 forms a complex with Vps34, Vps15, and Ambra1 [146]. Vps34 is a class III phosphatidylinositol 3-kinase, which generates phosphatidylinositol-3-phosphate PtdIns(3)P, required for the recruitment of further effectors [147]. Elongation of phogophore membrane is controlled by the conjugation of the adaptor molecule Microtubule-associated protein 1A/1B-light chain (LC3) to phosphatidylethanolamine (PE) forming a membrane-bound form LC3-II. Lipidated LC3-II mediates recruitment of

the autophagosomal membrane to the targeted mitochondria. LC3-II contains basic surface patches, which binds to CL [53] (Fig. 3). Reduced mitophagy has been observed in CL deficient cells [53]. Extending this concept, LC3B, a second member of the LC3 family also specifically interacts with externalized CL [148].

Apoptosis is a mechanism of controlled cell death, which is essential during cardiac development but also occurs in pathological conditions such as ischemia, infarction and in the end stage of heart failure [149]. Mitochondria play a prominent role as a signaling hub in the intrinsic apoptotic pathway, where diverse stimuli converge. An equilibrium of Apoptosis regulator Bcl-2 family proteins are an important regulator of apoptosis at the OM. Pro-apoptotic Bcl-2 family proteins, like Bax, Bak and Bid and anti-apoptotic Bcl-2 proteins, like Bcl-2, Bcl-XL, Bcl-W, and Mcl1 regulate the execution of apoptosis. CL plays a crucial role maintaining the delicate homeostasis of pro- and anti-apoptotic Bcl-2 proteins at the mitochondrion. During apoptosis active caspase-8 translocates to mitochondria dependent on the presence of CL on the outer mitochondrial membrane (Fig. 3). Caspase-8-mediated processing of Bid yields tBid, which is recruited to the OM by binding to CL. The binding of tBid to mitochondria was significantly decreased in CL deficient cells [55]. Also the subsequent recruitment and oligomerization of Bax and Bak in the outer mitochondrial membrane was found to be a CL dependent process [150–152]. The strict requirement of many apoptotic processes render lymphoblastoid cells from BTHS patients resistant to apoptotic triggers [57]. Accordingly, CL is an integral part of mitochondrial signaling and quality control pathways.

4. Pathophysiology of CL deficiency

4.1. Barth syndrome

Barth syndrome is caused by mutations in the X-linked CL remodeling enzyme Tafazzin [153]. Pathogenic mutations include missense, nonsense, splicing defects full or partial deletions and frameshift mutations [154–156]. Defects in CL remodeling causes an increase in MLCL and a decrease in mature forms of CL. The resulting increase in MLCL/CL ratios have been suggested for diagnosis of Barth syndrome [34,157]. Changes in mitochondrial morphology and disrupted cristae structures have been observed in BTHS mitochondria [158]. Rearrangement of the mitochondrial respiratory chain causes a decrease in respiratory chain supercomplexes, correlating with a decrease in respiration and reduced membrane potential in different models of BTHS [39,125,159]. Barth syndrome patients present with dilated or hypertrophic cardiomyopathy, or left ventricular myocardial noncompaction often associated with hypertrabeculation (“spongy myocardium”) [160]. Ventricular arrhythmia has also been described for BTHS patients [161], which may be a result of mitochondrial dysfunction or is associated with the cardiac phenotype [162,163]. Persistent or intermittent neutropenia is a common symptom and affects almost 70% of BTHS patients [164]. Patients present with a wide range of clinical findings with only mild reductions to strongly reduced levels of circulating neutrophils. However, in assays of neutrophil activity, including killing activity and directed motility, no significant decrease of neutrophil function was found [165]. Due to an increased Annexin V staining, an exposure of the apoptosis marker phosphatidylserine (PS) on cellular membranes has been suggested [165]. Increased apoptosis, however was not found in CL deficient neutrophils. Also, PS mediated clearance of CL-deficient neutrophils by activated macrophages was not detected in an *in vitro* setting [166]. Therefore, it appears that mitochondrial dysfunction causes a defect in the differentiation of neutrophils, similar to findings in Kostmann syndrome and Pearson syndrome [166]. However, bone marrow abnormalities or developmental defects of myeloid precursor cells were not found in BTHS [165]. Further common symptoms in BTHS also include skeletal myopathy, growth retardation and an abnormally high excretion of 3-methylglutaconic acid (3-MGA) [167]. 3-MGA excretion is highly variable [168] and results from 3-hydroxymethylglutaric acid, an intermediate of leucin breakdown pathway and cholesterol biosynthesis pathway.

Therapeutic strategies currently discussed involve interventions in the CL biosynthesis pathway in order to manipulate CL levels. In BTHS lymphoblasts a compensatory upregulation of MLCLAT1 has been observed. BTHS lymphoblasts transfected with a MLCLAT1 expression construct indeed rescued CL levels and reduced mitochondrial reactive oxygen species emission. However, the respiratory chain assembly defects were not restored [26]. As described above, remodeling of CL involves the hydrolysis of premature CL by phosholipase activity. A therapeutic approach in Tafazzin deficient animal models blocked phospholipase activity to rescue the existing CL pool. This strategy increased CL levels in patient lymphoblasts and reverted the male sterility phenotype in a tafazzin deficient *Drosophila* strain [23,169]. However, as the identity of the phospholipase for CL remodeling in mammals is unknown, therapeutic strategies are difficult to develop and inactivation of $iPLA_2\gamma$ function in BTHS mice did not prevent the decrease in tetralinoleoyl-CL [170]. Administration of linoleic acid as a precursor molecule for CL remodeling reestablished CL levels in BTHS fibroblasts [171] and sarcomere structure in BTHS iPSC derived cardiomyocytes [172]. Other therapeutic strategies target the emission of ROS by dysfunctional mitochondria. MitoTEMPO is an antioxidant compound, specifically targeted to mitochondria by triphenylphosphonium (TPP) in a membrane potential-dependent manner. MitoTEMPO reduced ROS production and improved sarcomere structure in iPSC derived cardiomyocytes from BTHS patients [172]. The Szeto-Schiller peptide (SS-31), is a tetrapeptide that accumulates in mitochondria based on its direct interaction with CL. Aromatic residues in SS-31 act as a ROS scavenger. SS-31 was shown to reduce CL-induced cytochrome *c* peroxidase activity, it improves IM cristae structures and reestablishes mitochondrial respiration [173]. These data indicate that ROS scavenging might be a promising strategy in the treatment of Barth syndrome.

4.2. Dilated cardiomyopathy with ataxia (DCMA)

DCMA patients present with dilated cardiomyopathy and in some cases with abnormalities in repolarization after a heartbeat (long QT syndrome, LQTS) [174]. Commonly described symptoms also include cerebellar ataxia, growth retardation, genital anomalies in male patients and 3-methylglutaconic aciduria [175]. A mutation in the gene encoding for the mitochondrial protein DNAJC19 was found to be causative for this disease [176]. DNAJC19 shares sequence similarities with the family of DnaJ proteins, which play a role as cofactors of Hsp70 chaperones. DNAJC19 displays particular similarity to the yeast protein Pam18/Tim14, which is an essential constituent of the presequence translocase associated motor complex (PAM). To this end, a function of DNAJC19 in protein import has not been shown. However, deletion of DNAJC19 in a cell model resulted in changes in the CL species composition without affecting total CL amounts [38]. Like in Tafazzin deficient cells, also DNAJC19 deficiency caused changes in mitochondrial cristae morphology. CL with four acyl esters adopts a cone shaped structure and possibly segregates into the cristae, which are membrane areas of locally high curvature. It has been speculated, that CL can even induce membrane bends and therefore directly contributes to mitochondrial morphology [177]. Mitochondrial morphology might be also shaped by the interaction of CL with the scaffolding protein prohibitin. Prohibitin oligomerizes into large ring like structures, which was suggested to restrict CL into specific membrane domains. While DNAJC19 binds to prohibitin, no interaction with Tafazzin was found. Therefore, the role of prohibitin appears to be to segregate specific membrane domains, which facilitate CL remodeling mediated by Tafazzin. This model explains the observed alterations in CL species composition found in DNAJC19 deficient cells.

4.3. Sengers syndrome

Sengers syndrome, is also known as cardiomyopathic mitochondrial DNA depletion syndrome-10 (MTDPS10). The clinical manifestation of the autosomal recessive disorder is dominated by a hypertrophic cardiomyopathy. Typical symptoms are also congenital cataracts, skeletal myopathy, exercise intolerance, and lactic acidosis. Similar to Barth syndrome, 3-methylglutaconic aciduria is also common in Sengers syndrome [178]. Decreased levels of mitochondrial adenine nucleotide translocator-1 (ANT) in heart and muscle tissues have been considered as a hallmark of Sengers syndrome [179]. As no mutations have been found in the *ANT* gene, it has been speculated that the transcription, translation, or posttranslational modification of ANT may be affected [180]. Mutations in the gene encoding for the mitochondrial acylglycerol kinase (AGK) were finally identified as causative for Sengers syndrome [181]. AGK is a mitochondrial lipid kinase strongly expressed in heart, but also in skeletal muscle, kidney and brain that can phosphorylate both monoacylglycerol and diacylglycerol to form lysophosphatidic acid (LPA) and phosphatidic acid (PA) [182,183]. PA is a precursor of CL and CL has been found to be essential for the structural integrity of ANT (see Section 3.3). Therefore, the function of AGK in the biosynthesis of CL explains well the initial finding of a defect in ANT in patients of Sengers syndrome. Since CL is essential for a large amount of mitochondrial functions, it is unlikely that defects in Sengers syndrome are restricted to a deficiency of ANT function. Analysis of mitochondrial respiration in muscle biopsies of patients revealed a respiratory defect, measurements of individual enzymatic functions showed a defect in complex I, III, IV, V and a compensatory increase in activity of complex II [181,184]. Abnormal mitochondrial morphology was found in both skeletal and heart muscle and fragmented mitochondria were found in cell lines [48,184]. Recent analysis of the interactome of AGK revealed a second unexpected function of the protein. AGK is a constituent of the mitochondrial carrier translocase, TIM22 complex (see Section 3.1). A defect in the import and assembly of carrier proteins has been found in AGK deficient mitochondria [48,75]. This function was found to be independent of AGK kinase activity. It can be assumed that loss of both functions in protein import and lipid biogenesis contributes to Sengers syndrome.

4.4. CL in ischemia/reperfusion, aging heart, and heart failure

Ischemia is a restriction of blood supply to tissues resulting in an insufficiency of oxygen and other nutrients and a failure in removing metabolic waste. Subsequent restoration of the blood flow (reperfusion) is associated with a high risk of oxidative damage. Ischemic heart disease is the leading cause of death in most western countries. Ischemia induces a loss of 20–25% of the CL amount in the heart. A global damage of cellular phospholipids has been documented, but the reduction of CL levels seems to precede losses in other phospholipids [185]. The production of ROS is well documented in ischemia/reperfusion injury [186] and increased levels of peroxidized CL were observed in the heart [187]. Enzymes of the phospholipase A family are involved in the specific degradation of oxidized CL and loss of CL was prevented upon ROS quenching [188]. Consistent with a decrease in CL levels also a decrease of the enzymatic activity of the cytochrome *c* oxidase without changes in its protein levels has been observed [189]. A change in CL species composition was not observed upon ischemia/reperfusion injury [185].

A reduction of CL content in mitochondria was also described in the aging heart [190]. Aging also caused changes in CL composition, which include a reduction of linoleic acid species and an increase in species with longer polyunsaturated acyl chains [191]. The longer polyunsaturated acyl chains might cause a stronger susceptibility of CL for peroxidation by ROS, and a faster degradation of peroxidized CL by enzymes of the phospholipase A family (see Section 3.2). Consistent with changes in the CL pool, defects in key mitochondrial functions have been observed. These include decreased activity of the mitochondrial phosphate transporter, pyruvate carrier, adenine nucleotide transporter and cytochrome *c* oxidase [192,193].

During heart failure (HF) in patients suffering from dilated or ischemic cardiomyopathies, cardiac CL content was reduced and changes in CL species composition became evident [194]. Changes in the CL pool have also been documented in animal models of heart failure. In a rat model of pressure-overload induced heart failure, a reduction in the content of CL was observed [195]. Spontaneously hypertensive HF (SHHF) rats show progressive changes in cardiac CL composition during the pathogenesis of HF. Linoleoyl-CL is strongly reduced in this model whereas CL species containing highly unsaturated acyl chains are increased. Consequently, a loss of cytochrome *c* oxidase activity was shown in this model [196]. These changes in the CL pool contribute to progressive decrease of mitochondrial function and to dramatic changes in energy metabolism, observed in cardiac disease.

5. Concluding remarks

Mitochondria have evolved from bacterial progenitor *via* symbiosis with a host cell. A large number of these ancestral qualities are still preserved in mitochondria including the production of ATP by oxidative phosphorylation, the mitochondrial genome and the phospholipid CL. Mitochondria have adapted to take over many more functions in cellular metabolism, in autophagy, in apoptosis and in cellular signaling pathways. During evolution, also CL acquired new essential roles in many of the mitochondrial functions. We highlight a structural role in the mitochondrial respiratory chain, in protein translocases and in mitochondrial carrier proteins. Four acyl chains form a strongly hydrophobic anchor and two negatively charged phosphate groups provide the basis for tight interaction with protein complexes. Besides structural contributions, CL also actively contributes to enzymatic reactions. This has been shown for its role in proton transport in complexes III and V reaction cycle. A resonance-stabilized structure facilitates CL function as a “proton trap”. A series of studies also revealed an independent role of CL in signal transduction processes. Under mitochondrial stress conditions CL is actively transported to the OM and exposed to serve as a binding site in many cellular signaling events. During mitophagy, CL recruits essential regulators. Apoptotic signaling pathways require CL as a binding platform. The two phosphate groups in CL are destined to forms electrostatic interactions with positively charged residues in target proteins [197,198]. However a uniform binding site has not been identified, possibly reflecting different types of interactions serving multiple different functions [199].

In an energy demanding process, CL remodeling shapes a tissue specific pool of CL species. A wide variety of hetero-acylated CL species is found in most tissues, whereas in heart tetralinoleoyl-CL predominates. It is currently unresolved why mitochondrial function in cardiac tissue requires a specific CL species composition. It has been speculated that protein complexes interacting with CL in the heart may have a specific requirement for CL. It is known that cardiac specific isoforms of structural subunits of the respiratory chain are found in close proximity to CL in the crystal structure. Therefore, CL may have specific functions in tissues with high energy demand like the heart. It will be necessary to better understand how CL acyl composition impacts different mitochondrial functions in different tissues and under different conditions. CL species shift towards longer and poly-unsaturated fatty acid chains in patients of dilated cardiomyopathy (DCM). Blocking the Delta-6-desaturase, responsible for the formation of poly unsaturated fatty acids, in a rat model of aortic pressure overload restored CL species composition, attenuated lipid peroxidation and preserved cardiac function [200]. Interestingly, inhibition of the Delta-6-desaturase to prevent long chain poly-unsaturated CL species in aging mice, also restored cardiac function, however without an effect on respiratory dysfunction, H_2O_2 emission and lipid peroxidation [201]. Recently, CL was identified as a precursor for lipid mediators whose physiological

roles are still obscure [202]. It can be speculated that a highly diversified CL pool may therefore be required for cellular communication. As substrate specificity of Tafazzin *in vitro* is very low the current view is that the physical state of the lipid environment determines the specificity of CL remodeling [37]. Further research will reveal how a specific lipid environment is formed allowing tissue specific CL remodeling.

A better understanding of the tissue specific CL biosynthetic pathway is essential for the development of novel therapeutic strategies. Some promising strategies have been developed in the past. Blocking the CL phosholipase activities in the CL remodeling pathway, which converts CL to MLCL has been used to explore a novel therapeutic approach to rescue the CL pool [23]. This strategy was able to rescue the male sterility in a tafazzin deficient Drosophila strain. Studies in yeast, in which the CL phospholipase was deleted by genetic intervention show that respiration remained preserved by a non-remodeled, premature pool of CL species [203]. However, inhibition of this enzyme in BTHS mice did not prevent the decrease in tetralinoleyl CL in cardiac tissue. Following another strategy, administration of linoleic acid as a precursor molecule for CL biosynthesis reestablished CL levels in fibroblasts from BTHS patients and rescued the sarcomere structure in patient derived cardiomyocytes [172]. An alternative approach, which is applicable in the context of diseases caused by dysfunctional mitochondria with an increased ROS burden, uses antioxidants, which are specifically targeted to mitochondria in order to preserve mitochondrial function from oxidative damage. In Barth syndrome cardiomyocytes the antioxidant MitoTEMPO induces a reorganization of sarcomeres and rescued the contractile function [172]. Another strategy utilizes the Szeto-Schiller peptide (SS-31), a tetrapeptide that accumulates in mitochondria due to its high affinity to CL through hydrophobic and electrostatic interactions. This peptide is already in clinical trials in patients with cardiovascular diseases [173].

Transparency document

The Transparency document associated with this article can be found, in online version.

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Conflict of interest

The authors declare no conflict of interest.

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