Received: 12 May 2021 | Revised: 28 July 2021 | Accepted: 19 August 2021

DOI: 10.1002/jimd.12427

REVIEW ARTICLE

JIMD SSIEM WILEY

Mechano-energetic aspects of Barth syndrome

Jan Dudek | **Christoph Maack**

Comprehensive Heart Failure Center (CHFC), University Clinic Würzburg, Würzburg, Germany

Correspondence
Jan Dudek, Department of Translational Research Comprehensive Heart Failure Center (CHFC), University Clinic Würzburg, Am Schwarzenberg 15, Haus A15, 97078 Würzburg, Germany.
Email: dudek_j@ukw.de

Funding information
Barth Syndrome Foundation; Deutsche Forschungsgemeinschaft; Deutsche Stiftung für Herzforschung (DE); German Federal Agency for Education and Research

Communicating Editor: Ronald JA Wanders

Abstract

Energy-demanding organs like the heart are strongly dependent on oxidative phosphorylation in mitochondria. Oxidative phosphorylation is governed by the respiratory chain located in the inner mitochondrial membrane. The inner mitochondrial membrane is the only cellular membrane with significant amounts of the phospholipid cardiolipin, and cardiolipin was found to directly interact with a number of essential protein complexes, including respiratory chain complexes I to V. An inherited defect in the biogenesis of cardiolipin causes Barth syndrome, which is associated with cardiomyopathy, skeletal myopathy, neutropenia and growth retardation. Energy conversion is dependent on reducing equivalents, which are replenished by oxidative metabolism in the Krebs cycle. Cardiolipin deficiency in Barth syndrome also affects Krebs cycle activity, metabolite transport and mitochondrial morphology. During excitation-contraction coupling, calcium (Ca^{2+}) released from the sarcoplasmic reticulum drives sarcomeric contraction. At the same time, Ca^{2+} influx into mitochondria drives the activation of Krebs cycle dehydrogenases and the regeneration of reducing equivalents. Reducing equivalents are essential not only for energy conversion, but also for maintaining a redox buffer, which is required to detoxify reactive oxygen species (ROS). Defects in CL may also affect Ca^{2+} uptake into mitochondria and thereby hamper energy supply and demand matching, but also detoxification of ROS. Here, we review the impact of cardiolipin deficiency on mitochondrial function in Barth syndrome and discuss potential therapeutic strategies.

KEYWORDS

Barth syndrome, cardiolipin, mitochondria, reactive oxygen species, respiratory chain

1 | INTRODUCTION

The heart gains on average 6 kg of ATP in 1 day by converting energy stored in fatty acids, lactate, glucose, ketones and amino acids into mechanical work. 95% of this energy demand is covered by oxidative phosphorylation.[1] Oxidative metabolism of fuels, especially in the Krebs cycle of mitochondria, produces the reducing equivalents NADH and $FADH_2$ which are utilized by the respiratory chain. The five complexes of the respiratory chain are involved in electron transport from reducing equivalents onto molecular oxygen (O_2). The

electron transport through complexes I, III and IV is coupled with proton export across the IM, generating a proton gradient (ΔpH) which together with the electrochemical potential ($\Delta\Psi_m$) constitutes the proton motive force ($\Delta\mu_H$) that is harnessed for the production of ATP by the F_1F_o-ATP synthase. The mitochondrial creatine kinase uses ATP to form phosphocreatine (PCr), which serves as an easily diffusible energy buffer to support myofilament activity. Under physiological conditions, cardiac workload is increased by β-adrenergic activation, which increases the amplitude and frequency of cytosolic Ca^{2+} transients. Ca^{2+} is also transmitted into mitochondria, where it serves to activate the Krebs cycle in order to compensate for the increased energy demand.[2] 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.

Mitochondria are double membrane surrounded organelles. The outer membrane (OM) has various interactions to other organelles in the cell, including the sarcoplasmic reticulum (SR), the lysosome and the plasma membrane.[3-5] The inner mitochondrial membrane (IM) separates the intermembrane space (IMS) from the matrix compartment. Cristae structures are invaginations of the IM and harbor the respiratory chain. Compared to other cellular membranes, the IM has a profoundly different phospholipid composition, as it contains large amounts of cardiolipin (CL) as an archetypal phospholipid.[6] Defects in the CL pool are observed in many forms of heart disease, including myocardial infarction, diabetic cardiomyopathy and the aging heart.[7-9] Moreover, defects in the CL biosynthesis are linked to inherited diseases, including Sengers disease, Dilated Cardiomyopathy with Ataxia (DCMA) and Barth syndrome.[7,10,11] Barth syndrome (BTHS) (OMIM 302060) is an X-linked disease, caused by a mutation in the gene *Taz/Tafazzin*.[12,13] BTHS has an estimated incidence of 1/300 000-400 000 births and is associated with cardiomyopathy, skeletal myopathy, neutropenia, growth retardation, and 3-methylglutaconic aciduria. The gene *Taz/Tafazzin* encodes for tafazzin, which is a mitochondrial acyltransferase involved in the remodeling of cardiolipin (CL). In this review, we will discuss the many functions of CL in mitochondrial morphology, mitochondrial metabolism, and respiration. Furthermore, we will discuss how defects in CL biosynthesis and remodeling affect mitochondrial energy conversion and redox homeostasis. Finally, we discuss the clinical picture of Barth syndrome and other related diseases and how therapeutic approaches may ameliorate these severe diseases, which are so far largely orphaned from efficient treatment.

2 | THE CLINICAL PRESENTATION OF BTHS PATIENTS

The most common feature of BTHS is cardiomyopathy which is commonly diagnosed within the first 5 years of life and requires cardiac transplantation in severe cases.[14-16] The cardiac phenotype is quite variable and includes dilated cardiomyopathy, left ventricular noncompaction, endocardial fibroelastosis, ventricular arrhythmias, and sudden cardiac death.[16] A subset of patients only shows mildly abnormal cardiac function.[15] In these patients, left ventricular ejection fraction (LVEF) averages at ~50% without signs of further deterioration over time.[16] These BTHS patients suffer from exercise intolerance, and a particular defect in adjusting cardiac output to changing workload conditions.[17] Moreover, the risk of ventricular arrhythmia and sudden cardiac death is increased in BTHS.[18] BTHS is a multisystem disorder, which includes skeletal myopathy and delayed motor development.[15,19] BTHS patients are strongly affected by fatigue and exercise intolerance, which is not only due to the diminished cardiac contractile reserve but also due to reduced skeletal muscle oxygen extraction.[17] Glucose turnover rate is significantly higher and fatty acid oxidation is reduced upon exercise in BTHS patients. These studies indicate that the metabolic response to exercise is severely blunted, which contributes to an energetic deficit and a decreased exercise capacity in BTHS.[20]

Persistent or intermittent neutropenia in BTHS patients causes recurrent infections and are the second common cause of hospitalization in BTHS patients.[15,16,21] Interestingly, neutrophil function is unaffected in vitro, and neutrophils from BTHS patients have normal mitochondrial morphology and show preserved vital functions. Other studies reported on lower numbers of CD8+ T cells and reduced IFNγ production upon stimulation.[22,23] Metabolic changes in BTHS are manifested by increased levels of 3-methylglutaconic acid (3-MGA) excretion in the urine.[24,25] 3-MGA is an intermediate in the metabolism of cholesterol and the branched-chain amino acid leucine. Amino acid metabolism is severely remodeled in BTHS, indicated by abnormal blood levels of amino acids, in particular reduced plasma levels of arginine.[26-28] However, 3-MGA levels have been reported to be independent of leucine metabolism.[29] BTHS patients have decreased levels of low-density lipoprotein (LDL) cholesterol and hypocholesterolemia.[30] As cholesterol biosynthesis also originates in mitochondria, mitochondrial dysfunction due to CL deficiency might impair this process, and these defects of sterol and isoprenoid metabolism may be associated with elevated 3-MGA levels.

3 | THE ROLE OF TAFAZZIN IN CARDIOLIPIN REMODELING

CL biosynthesis resides in the inner mitochondrial membrane (Figure 1). CL biosynthesis starts with the precursor molecule phosphatidic acid (PA). PA is either imported from the endoplasmatic/sarcoplasmic reticulum (ER/SR) or provided by the acylglycerolkinase (AGK), which phosphorylates diacylglycerol (DAG) to provide PA.[31-34] PA is subsequently activated with cytidine triphosphate (CTP) by the phosphatidate cytidylyltransferase TAMM41.[35] The CDP-diacylglycerol-glycerol-3-phosphate 3-phosphatidyltransferase PGS1 catalyzes the reaction with glycerol-phosphate to phosphatidylglycerol phosphate, which is subsequently dephosphorylated by the phosphatidylglycerophosphatase and protein-tyrosine phosphatase 1 PTPMT1.[36-38] Knockout of PTPMT1 or chemical inhibition by alexidine dihydrochloride (AD) stops the maturation of CL and impairs the assembly of ETC complexes, leading to increased generation of ROS (Figure 1).[22,39] With the reaction of phosphatidylglycerol with a second molecule of CDP-DAG, catalyzed by the CL synthase (CLS1), premature CL is produced, which lacks a tissue-specific fatty acid species composition.[40-42] Therefore, premature CL (pCL) undergoes a remodeling step, in which a tissue-specific acylation pattern is formed. The initial deacetylation of CL is catalyzed by a yet unidentified member of the Ca^{2+}-independent phospholipases, which can be blocked by the inhibitor bromoenol lactone (BEL) (Figure 1). The subsequent reacetylation is catalyzed by one of three enzymes including monolysocardiolipin (MLCL) acyltransferase (MLCLAT1), acyl-CoA:lysocardiolipin acyltransferase (ALCAT1), or tafazzin.[43-47] The severe cellular defects in BTHS suggest tafazzin as a key enzyme in CL remodeling under physiological conditions. Tafazzin enzymatic activity is described as a coenzyme A independent acyltransferase, exchanging fatty acids between phospholipids and lysophospholipids. In contrast to many other transacylases, tafazzin does not form an enzyme-acyl intermediate, but its HX4D motif enables the direct transfer of acyl groups onto lysophospholipids bound to the active site in the enzyme.[48] Defects in the tafazzin mediated CL remodeling causes an increase in the CL precursor MLCL and a decrease in total CL amounts and in mature CL species. The resulting increase in MLCL/CL ratios can be used as a diagnostic marker for Barth syndrome.[49,50] MLCLAT-1 may play a complementary role in CL remodeling, as overexpression of MLCLAT-1 in BTHS lymphoblasts improved ROS emission, however besides increasing total CL levels it neither restored CL acylation pattern nor improved respiratory chain remodeling.[51] ALCAT1 plays a role in catalyzing the acylation with unsaturated long-chain fatty acids, which are prone to peroxidation. ALCAT1 was found to play a role to generate a peroxidation prone CL pool in context of diet induced obesity in mouse.[7,44] CL has a relatively long half-life compared to other phospholipids.[52-54] The slow turnover of CL was explained by its tight interactions with the respiratory chain.[55] When this association is lost, CL may become more susceptible to degradation, contributing to low CL levels in BTHS. Kinetic analyses found that the biosynthesis rate was unaffected in patient skin fibroblasts despite lower CL levels, supporting the model of accelerated degradation. The enzymes involved in CL elimination are not identified yet. Suggested candidates include the cytosolic PLA2 (cPLA2)[56] and the mitochondrial splice

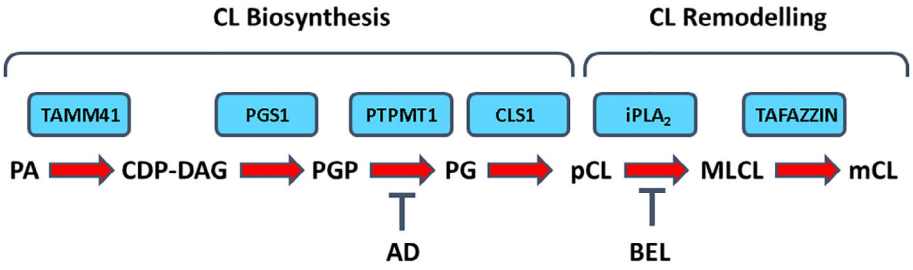

FIGURE 1 CL biosynthesis and remodeling in the inner membrane. Phosphatic acid (PA) and cytidine triphosphate (CTP) are converted to CDP-DAG by the CDP-DAG synthase TAMM41. The phosphatidylglycerol phosphate synthase 1 (PGS1) catalyzes the reaction of CDP-DAG and glycerolphosphate to form phosphatidylglycerol phosphate (PGP). PGP is then dephosphorylated by the mitochondrial protein-tyrosine phosphatase 1 (PTPMT1) to form phosphatidylglycerol (PG). The cardiolipin synthase 1 (CLS1) catalyzes the second addition of CTP to form premature CL. The PTPMT1 inhibitor AD and the inhibitor of the calcium-independent phospholipases BEL is indicated. CL remodeling is initiated by elimination of fatty acids (FAs) mediated by a member of the phospholipase iPLA2 family to from monolysocardiolipn (MLCL). In the last step tafazzin catalyzes the incorporation of new FAs and the formation of mature CL. TAMM41: CDP-DAG synthase, CDP-DAG: cytidindiphosphate-diacylglycerol, PGS1: phosphatidylglycerol phosphate synthase, PGP: phosphatidylglycerol phosphate, PTPMT1: protein-tyrosine phosphatase mitochondrial 1, PG: phosphatidylglycerol, CLS1: cardiolipin synthase, iPLA2/iPLA2γ/iPLA2-VIA/HSD10: calcium-independent phospholipases, AD: alexidine dihydrochloride, BEL: bromoenololactone

variant cPLA2β3,[57] the phospholipase HSD10 and the phospholipase D (MitoPLD).[58]

CL biosynthesis initiates from its precursor molecule PA. PA is efficiently transported from the ER with the help of two proteins PRELID1 and TRIAP1, which form a heterooligomeric complex in the IMS. The formation of this complex enables PRELID to extract PA from the outer membrane. Structural analysis in yeast suggests the coordination of a PA molecule in a central hydrophobic cavity of the PRELID1-TRIAP1 complex.[59] After its transport across the intermembrane space and upon binding to the IM, the complex associates with the IM, is destabilized and TRIAP1 released. This allows PRELID to interact with the IM and to release PA. The rapid turnover of PA to CL supports the directionality of the transport reaction. Increasing CL concentrations cause PRELID degradation by the i-AAA protease, regulating CL accumulation in the inner membrane.[60]

In the "dimeric" structure of CL, two phosphatidic acid moieties bond with a central glycerol backbone. Therefore, CL possesses four different fatty acids, which differ in length and saturation, forming a diversified CL pool in different tissues.[61] The characteristic CL pool of the heart consists mostly of tetralinoleoyl-CL (CL (18:2)).[62] The CL acylation pattern is important for the biochemical properties of this lipid within the membrane.[63] Despite the tissue specificity of the CL pool, the substrate specificity of tafazzin is very low in vitro. It has been suggested that the substrate specificity of tafazzin is determined by the physical properties of the membrane. Large protein structures like the respiratory chain induce elastic stress in the molecular packing of lipids. The enzymatic activity of tafazzin catalyzes the remodeling of CL, which allows the membrane to release packing stress and to strive towards an energetic minimum. The particular density of the respiratory chain complexes in cardiac tissue might therefore explain the preferential incorporation of distinct acyl chains into cardiac CL species.[64,65] This also explains that tafazzin activity supports different CL compositions in different tissues. In contrast to its role in maintaining CL with unsaturated fatty acids in heart tissue, tafazzin knockdown in acute myeloid leukemia (AML) cells produced CL acyl species with more than 5 double bonds and longer chains.[66]

It is increasingly recognized that tafazzin deficiency also affects other phospholipid species. In cardiac tissue of the tafazzin deficient mouse model, increased linoleic acid content in phosphatidylcholine and an increase in arachidonic acid in phosphatidylethanolamine was reported.[67] Tafazzin knockdown in acute myeloid leukemia (AML) cells decreased levels of cardiolipin, as well as phosphatidylethanolamine (PE) and increased levels of phosphatidylserine (PS). The mechanism here was found in the PS decarboxylase (PISD), which converts PS to PE in the IM. As recombinant PISD binds preferentially to cardiolipin, and knockdown of tafazzin decreased protein levels of PISD, it was concluded that reduced PS conversion contributes to the phospholipid shift in AML cells.[66] Furthermore, decreased levels of plasmalogens in heart, liver, kidney, brain and lymphocytes are documented in the BTHS mouse model.[68] Interestingly, plasmalogens are ether lipids and prone to oxidation. Being preferentially oxidized when exposed to ROS, plasmalogens thereby act as "sacrificial oxidants" and spare the oxidation of other membrane lipids.[69] Therefore, a possible explanation for decreased plasmalogen levels in BTHS is their increased turnover after oxidation by a higher oxidative burden in BTHS mitochondria.

4 | CARDIOLIPIN SHAPES MITOCHONDRIAL MORPHOLOGY

Maintaining morphology is essential for mitochondrial function, and defects in morphology promotes apoptosis and cell death.[70] In adult cardiomyocytes, mitochondria are aligned longitudinaly between myofilaments ("interfibrillar"), are located underneath the sarcolemma ("subsarcolemmal") or locate around the nucleus ("perinuclear"). Heart failure is often associated with defects in mitochondrial dynamics and changes in mitochondrial morphology.[71] Increased mitochondrial fragmentation has been described in diabetic cardiomyopathy[72] and ischemia/reperfusion injury.[73-77] Also in BTHS, morphological alterations have been described in patients as well as in animal models of tafazzin deficiency. Mitochondrial enlargement, concentric layers of cristae or large vacuoles were observed in cardiac muscle of tafazzin-deficient mice.[78] BTHS patient-derived lymphoblasts reveal enlarged, sometimes giant, mitochondria with substantial changes in the cristae structure.[79,80] CL is involved with many of the molecular processes shaping mitochondrial morphology.

In most cell types, morphology of mitochondria is maintained by fission (segregation) and fusion (merging) of individual mitochondria which allows mixing of mitochondrial content,[81] and proteins involved in fission and fusion are highly expressed in cardiomyocytes.[82,83] The dynamin-related GTPases Mfn1, Mfn2, OPA1 and Drp1 are involved in regulating the morphology of mitochondria. Fusion of mitochondria is mediated by mitofusins (Mfn) 1 and 2 and OPA1. Mfn1 and Mfn2 are located on the outer mitochondrial membrane.[84] The formation of hetero-oligomers tethers the outer membranes of opposing organelles and initiates membrane fusion. Mfn1 mediated fusion is activated by PA, which is produced by the specific turnover of CL by the phospholipase

MitoPLD[85] (Figure 2). The phospholipase PA-PLA1 or the phosphatase Lipin 1b hydrolyzes PA and antagonizes PA-mediated activation of mitofusins.[86] OPA1, located in the inner membrane, regulates the fusion of the inner membrane.[87] Alternative splicing and proteolytic processing form long and short forms, which assemble into dimeric complexes that regulate mitochondrial morphology.[88] Imbalanced OPA1 processing in cardiac tissue can cause metabolic remodeling of the heart, resulting in dilated cardiomyopathy.[89] CL promotes dimerization and induction of OPA1 GTPase activity and acts as a binding receptor on the opposing mitochondrion, which binds to the IMS domain of OPA1.[90-92]

Mitochondrial fission receptors, like Fis1, MFF, MiD49 and MiD51[93] recruit cytosolic Drp1 to the mitochondrial outer membrane (Figure 2). The dynamin related GTPase Drp1 is an important mediator of mitochondrial fission. Oligomerization of Drp1 into helical structures constricts the outer membrane. Drp1 is regulated by a small unstructured variable domain (VD), which directly interacts with CL and promotes the oligomerization of Drp1.[94-96] Decreased levels of Mfn2 and OPA1 and increased levels of Drp1 was observed in human heart failure patients. Application of the CL-interacting molecule SS31/Elamipretide normalized the deregulation of proteins in human heart failure patients.[97]

Mitochondria interact closely with other organelles in the cell, including lysosomes,[98-100] peroxisomes[101,102] and the ER. Mitochondria-associated membranes (MAMs) approximate ER membranes to a distance of ~10 to ~50 nm.[103] A structural bridge between these organelles is formed by Mfn2, which localizes partially also on the ER membrane and interacts with Mfn1 on the mitochondrial outer membrane.[104] The ER-mitochondria communication is essential for adequate Ca^{2+} signaling. Ablation of Mfn2 caused decreased mitochondrial Ca^{2+} uptake and reduces Ca^{2+} induced stimulation of the Krebs cycle.[105] The outer mitochondrial membrane protein FUNDC1 is highly expressed in cardiac tissue, and recent evidence suggests that its interaction with the IP_3 Receptor (IP_3R) in the ER contributes to the tethering of both organelles.[106]

Mitochondrial cristae emerge from the inner boundary membrane (IBM) into the matrix (Figure 3). Crista junctions (CJs) play a particular role as diffusion barriers, which segregate proteins involved in membrane fusion and protein import in the IBM and proteins of the respiratory chain in the cristae membranes. Thereby individual cristae act as independent bioenergetic units with different membrane potentials.[107] The mitochondrial contact site and cristae organizing system (MICOS) plays a particular role in the structural organization of CJ (Figure 3)[108] and allows to dynamically change their structure depending on their metabolic state. CL stabilizes the oligomerization of Mic10, a central component of the Mic10/Mic26/Mic27-subcomplex.[109] MIC26/Apolipoprotein O and Mic27/Apolipoprotein O-like belong to the family of lipid binding apolipoproteins. Mic27 binds to CL in vitro, and CL stabilizes the MICOS complex.[109-111] Interestingly, the levels of Mic26 and Mic27 are positively correlated with protein levels of tafazzin.

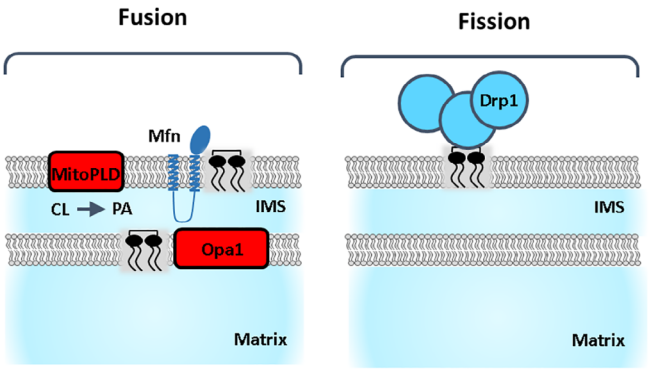

FIGURE 2 Role of CL in mitochondrial morphology. The morphology of the mitochondrial network is maintained by fission and fusion. Upon recruitment of cytosolic GTPase Drp1 to the outer membrane cardiolipin (CL) enhances the oligomerization required for fission of mitochondria. Mitochondrial fusion of the outer membrane is mediated by mitofusins (Mfn). The phospholipase MitoPLD converts CL into phosphatidic acid (PA), which promotes mitofusins mediated fusion. For fusion of the inner mitochondrial membranes the GTPase Opa1 is required. CL promotes dimerization and induction of Opa1 GTPase activity OM: outer mitochondrial membrane, IMS: intermembrane space

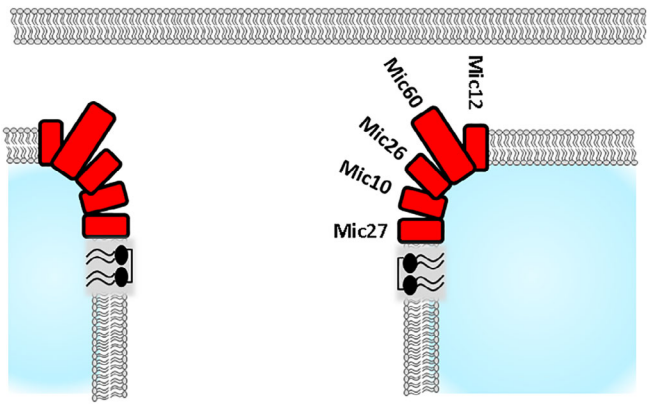

FIGURE 3 Role of CL in MICOS assembly. Mitochondrial cristae are maintained by the MICOS complex, consisting of the proteins Mic27, Mic10, Mic26, Mic60, and Mic12. The complex resides at the cristae junctions of the inner membrane. CL was shown to bind to Mic27 and to stabilize stabilizes the MICOS complex

Mic26 and Mic27 strongly cooperate in maintaining CL levels and are required for integrity and stability of the respiratory chain complexes.[112] Since in BTHS, mitochondrial morphology and in particular, cristae structure is altered, it is also conceivable that the MICOS complex is altered. In fact, complexome analyses of BTHS patient skin fibroblasts revealed a shift towards higher molecular weight forms of this complex, indicative for structural complex remodeling. Surprisingly, this study also found increased abundance of the MICOS complex components, which may be explained by a compensatory increase of gene expression.[113]

5 | THE ROLE OF CARDIOLIPIN IN MITOCHONDRIAL METABOLISM

Membrane protein complexes interact in multiple ways with the phospholipid bilayer. Direct interactions affect conformation, oligomerization, stability and activity of proteins. Indirect effects include biochemical properties of the membrane, such as curvature, thickness, surface charge and lipid packing density, which also affects membrane protein properties.[114,115] Changes in the structure of the respiratory chain complexes due to the absence of CL is intensively studied in BTHS. CL plays a role in the structural integrity and enzymatic activity of all five complexes of the respiratory chain (Figure 4). Structural analysis revealed specific binding sites for CL in all complexes of the respiratory chain (complex I,[116] complex III,[117,118] and complex IV[119]). An active role of CL in the enzymatic activity has been particularly suggested for complexes III, IV, and V.[120-122] Finally, CL facilitates the formation of respirasomes, which are large supercomplexes (I, III, and IV) in a defined stoichiometry.[123-126] The close proximity of the complexes in respirasomes increases the efficiency of the electron translocation and minimizes the risk for the generation of ROS.[127-130] Analysis of BTHS mitochondria indicates structural remodeling of the respiratory chain and a shift from high to low molecular weight complexes. CL deficiency also affects the enzymatic activity of individual complexes in the respiratory chain.[131-133]

Several enzymes of the Krebs cycle are also associated to the inner membrane and are affected by CL deficiency (Figure 4). The α-ketoglutarate dehydrogenase complex is tightly associated with the matrix side of the IM and serves as the entry point of α-ketoglutarate, derived from glutamate into the Krebs cycle.[134] This complex was found to be structurally affected in human BTHS patient fibroblasts, without a measurable decrease in its enzymatic activity.[113] The succinate dehydrogenase (complex II) is an integral complex in the IM and reduced amounts of this complex result in reduced enzymatic activity in BTHS.[132,135] Changes in the enzymatic activities of aconitase were also reported in BTHS.[135] In agreement with reduced aconitase and succinate dehydrogenase activity, metabolic flux analyses detected increased levels of citrates and decreased level of fumarate in BTHS induced pluripotent stem cell derived cardiomyocytes (iPSC-CM).[136] In order to cover the metabolic demands in the mitochondria, an intensive exchange of metabolites across the IM is necessary, mediated by the family of

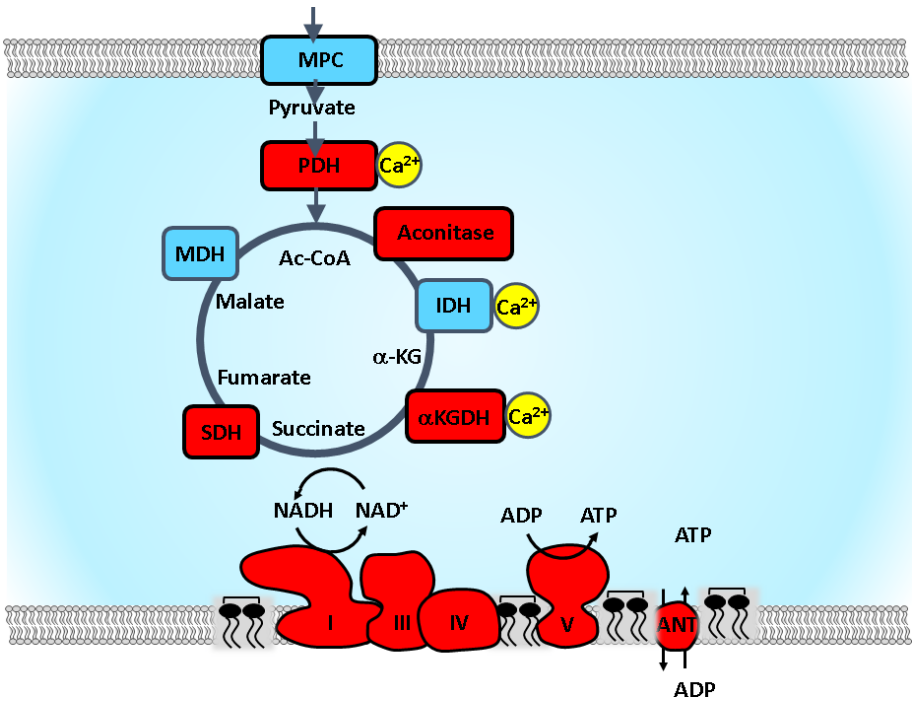

FIGURE 4 CL is involved in respiration and Krebs cycle. The mitochondrial respiratory chain complexes I, III, and IV assembles into large oligomeric structures, called respirasomes. CL plays an essential role in respirasome formation and activity. CL also interacts with mitochondrial carrier proteins such as the ADP/ATP carrier. Essential functions of the Krebs cycle, including the α-ketoglutarate dehydrogenase (αKGDH), succinate dehydrogenase (SDH) and aconitase are defect in CL deficient cells. CL molecules partially interacting with membrane protein complexes are shown in red. ANT, ADP/ATP carrier, MPC, mitochondrial pyruvate carrier; Cyt c, Cytochrome c; IM inner membrane; IMS, intermembrane space

carrier proteins. The ADP/ATP carrier (ANT) is the most abundant carrier protein and tightly interacts with CL in the crystal structure.[137-139] Also, the phosphate carrier (PiC), the monocarboxylate carrier (MCT1), the carnitine/acylcarnitine translocase, the pyruvate carrier and the tricarboxylate carrier[140-142] belong to the family of carrier proteins and it has been suggested that also these complexes require CL for their activity.

Incomplete reduction of oxygen by the transfer of less than four electrons causes the emission of ROS from the cell. The respiratory chain and in particular, complexes I and III are the main producers of ROS. Due to the structural changes of the respiratory chain in BTHS, ROS production has been intensively studied. Whether ROS emission in BTHS is increased is controversially discussed, currently. Tafazzin deficient yeast shows increased levels of protein carbonylation, indicative of increased ROS production.[143] Immortalized lymphoblasts from BTHS patients have slightly increased basal superoxide levels than control cells.[80] ROS levels have been also intensively studied in cardiac myocytes. In patient-derived and genetically engineered (iPSC-CM), sparse and irregular sarcomeres were documented, which correlated with a weaker contractility in a "heart-on-chip" model. Resolving excess levels of ROS with the scavenger mitoTEMPO rescued the sarcomere disarray and improved systolic function.[144] Similarly, mito-Tempo normalized mitochondrial ROS production and rescued cardiac hypertrophy and contractile dysfunction in cardiac myocytes with reduced tafazzin expression.[145] While all these studies show increased ROS levels, the effect on heart function remains controversial. In a tafazzin-deficient mouse model, mitochondrial targeted catalase (mCAT) was overexpressed. Mitochondrial H_2O_2 emission and lipid peroxidation were increased in tafazzin deficient mice, and this was normalized by overexpressing mCAT. However, no difference in the development of cardiomyopathy and muscle weakness was found. Also, despite resolving oxidative stress, there was no improvement in cardioskeletal myopathy.[146] In contrast to the studies discussed above, a recent study did not detect any increase in ROS production in a mouse model of BTHS. The study tested 11 potential sites of superoxide and H_2O_2 production in isolated mitochondria from heart and skeletal muscle from tafazzin deficient mice at different ages. As there was no elevated ROS production in heart tissue, the authors concluded that mitochondrial ROS production unlikely contributes to the development of cardiomyopathy in this mouse model.[147] In hypoxia, where a reverse electron flux through complex I triggers a strong increase in ROS, ROS production is even decreased in a tafazzin deficient mouse embryonic mouse model.[148]

One potential reason for the different results is that the emission of ROS depends on the balance between ROS production and elimination, and these processes depend on the metabolic state of the cell. Superoxide is produced at the respiratory chain, particularly when the respiratory chain is highly reduced.[149,150] A structural transition towards an inactive state of complex I is involved in reducing ROS under conditions of ischemia. Whether CL is involved in this protective deactivation of complex I is not known. Superoxide is efficiently removed by the superoxide dismutase, forming H_2O_2, which is then converted to water by glutathione peroxidase (GPX) and peroxiredoxin (PRX).[151] These enzymes are dependent on glutathione (GSH) and thioredoxin (TRX), respectively, which is regenerated by NADPH.[152] NADPH is regenerated by enzymes, which are fueled by the Krebs cycle: $NADP^+$-dependent isocitrate dehydrogenase (IDP), malic enzyme and the nicotinamide nucleotide transhydrogenase (Nnt). Therefore, the redox state also strongly determines the ROS defense mechanisms. Consequently, under conditions of more oxidized redox state, superoxide production at the respiratory chain is lower, but antioxidative capacity is also diminished.[153,154] The balance of ROS production and elimination might be optimal within a narrow range of an intermediate redox potential.[153]

6 | DOES CARDIOLIPIN MODULATE CALCIUM SIGNALING?

Ca^{2+} is an essential regulator of excitation contraction coupling in the heart. During the action potential, Ca^{2+}enters cardiac myocytes via L-type Ca^{2+} channels and activates ryanodine receptors (RyR2) to release Ca^{2+} from the sarcoplasmic reticulum (SR). Ca^{2+} release triggers Ca^{2+} binding to troponin C and induces contraction. During diastole, Ca^{2+} is rapidly exported across the cell membrane via the Na^+/Ca^{2+} (NCX) exchanger and transported back into the SR via the SR Ca^{2+}-ATPase (SERCA).[155] SERCA plays an important role in diastole as it ensures sufficient Ca^{2+} load in the SR and allows muscle relaxation before the next systolic contraction. Decreased SR Ca^{2+} load is associated with many forms of heart failure, including dilated cardiomyopathy.[156,157] In a recent study in BTHS iPSC-CM, increased ROS levels were shown to activate Ca^{2+}/calmodulin-dependent protein kinase II (CamKII). CamKII mediated phosphorylation of RYR2 causes SR Ca^{2+} leak and contributes to reduced systolic Ca^{2+} transients and increased diastolic Ca^{2+} levels in BTHS iPSC-CM and cardiomyocytes with a cardiomyocyte specific tafazzin knockout. Altered Ca^{2+} handling contributes to an increased arrhythmia

propensity in these BTHS models.[158] During each cytosolic Ca^{2+} transient, Ca^{2+} is transmitted from the SR to the mitochondrial matrix via MCU being in close association with the RyRs of the SR, so-called SR-mitochondrial Ca^{2+} microdomains.[159] Transmission of Ca^{2+} into mitochondria allows for mitochondrial Ca^{2+} homeostasis and for the adaptation of mitochondrial metabolism with cellular workload. Increases in cardiac workload accelerate the turnover of ATP to ADP (Figure 5). The increased ATP demand stimulates the activity of the mitochondrial respiratory chain via ADP and enhances the turnover of reducing equivalents. The higher demand for reducing equivalents is compensated by a higher activity of the dehydrogenases in the Krebs cycle.[160] Ca^{2+} plays an important role in activating Krebs cycle dehydrogenases, including pyruvate dehydrogenase, isocitrate dehydrogenase and α-ketoglutarate dehydrogenase. By accelerating the regeneration of NADH and $FADH_2$, Ca^{2+} secures mitochondrial energy conversion. NADH regeneration is also important to maintain the antioxidative capacity. Glutathione peroxidase and peroxiredoxins require NADPH, which is regenerated in an NADH dependent manner by the nicotinamide nucleotide transhydrogenase (NNT), which preferentially accepts NADH from the α-ketoglutarate dehydrogenase, as well as isocitrate dehydrogenase and malic enzyme.[161] Therefore, a transmission of cellular Ca^{2+} into mitochondria allows a tight coupling of energy supply and demand as well as antioxidative capacity with cellular work.[159]

The transmission of Ca^{2+} from the SR into the mitochondria requires a tight structural association of RyR2 in the SR and the mitochondrial Ca^{2+} Uniporter (MCU) in mitochondria.[162] As Mfn2 interaction is an important structural link between mitochondria and the SR, it was speculated that a defective contact site might impair mitochondrial Ca^{2+} signaling (Section 4). However, recent investigations shed light into a more direct link of CL and mitochondrial Ca^{2+} uptake. The MCU complex consists of an oligomer of the protein MCU associating with EMRE and the regulatory subunits MICU1, MICU2, and MCUb.[163-167] The regulatory subunits MICU1 and MICU2 keep the MCU channel closed at low Ca^{2+}

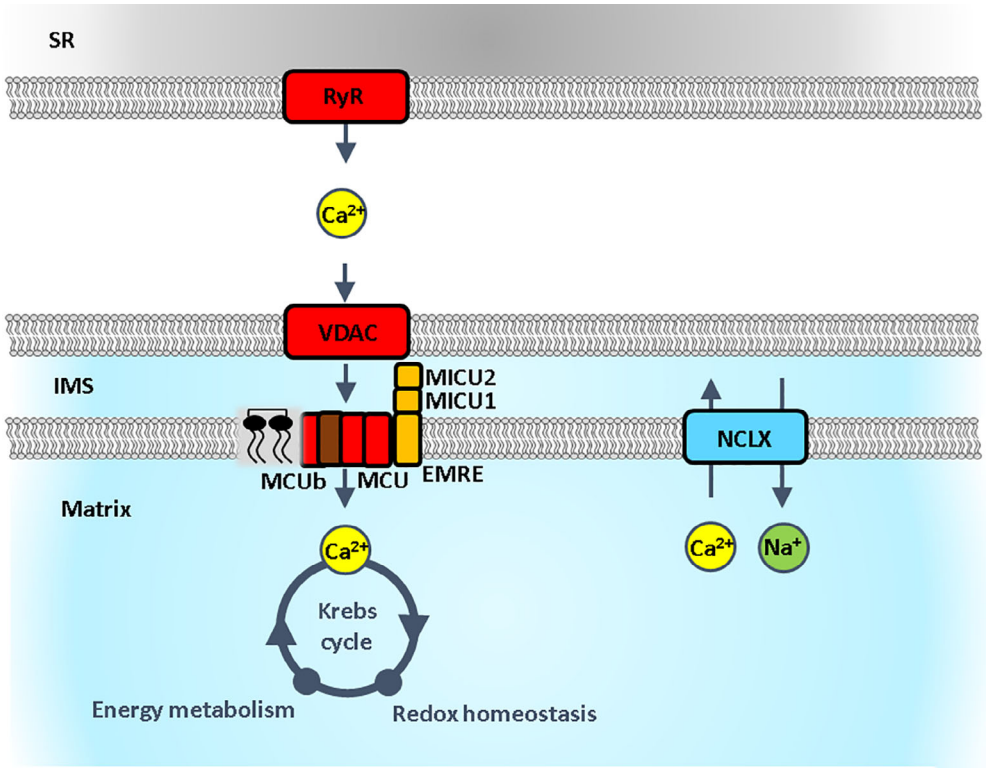

FIGURE 5 Calcium release from the SR and mitochondrial energy production. Calcium released from the sarcoplasmic reticulum via RyR is transmitted into mitochondria. A close proximity of RyR and the mitochondrial calcium uniporter (MCU) allows the direct transmission of calcium into the mitochondrial matrix. Calcium activates matrix calcium-dependent dehydrogenases in the Krebs cycle and induces synthesis of intracellular ATP to support cardiac contraction. Calcium export is mediated via the NCLX sodium exchanger. ATP, adenosine triphosphate; MCU, mitochondrial calcium uniporter; NCLX, mitochondrial sodium/calcium exchanger; SR, sarcoplasmic reticulum; RyR, ryanodine receptors; IMM, inner mitochondrial membrane; OMM, outer mitochondrial membrane; ROS, reactive oxygen species

concentrations and induce activation of the channel upon elevated Ca^{2+} concentrations.[168] Structural analyses revealed specific binding of CL to the MCU complex.[169,170] While these studies showed a direct interaction of CL with EMRE, also a binding of CL with the MCU protein was recently suggested.[171] Furthermore, CL also interacts with the regulatory subunits MICU1 and MICU2 in vitro,[172] indicating that CL has several interaction sites in the MCU complex. CL was found to play an essential role for the stability and activity of the MCU complex. Consequently, B-lymphoblasts and cardiac tissue of BTHS patients have reduced amounts of MCU.[171] It can be speculated that the absence of MCU causes a defect in the regeneration of reducing equivalents in tafazzin deficient mice. This is supported by studies on cardiac myocytes from guinea pig using pharmacological inhibition of MCU or acceleration of Ca^{2+} efflux by NCLX. Inhibition of mitochondrial Ca^{2+} influx caused a defective regeneration of NAD(P)H and increased levels of H_2O_2 emission.[173,174] Similarly, MCU deficient mouse hearts show no defect in NADH regeneration at rest but a significant defect under conditions of increased workload.[175] However, to resolve this in more detail, further studies are required to address the functionality of bioenergetic coupling in tafazzin-deficient cardiac myocytes.

7 | THE MANY ROLES OF CARDIOLIPIN IN STRESS RESPONSE

Autophagy is an essential quality control mechanism as it allows the bulk degradation of damaged or superfluous cytoplasmic components. Autophagy is essential to maintain cardiac function under basal conditions in the adult heart.[83,176-178] Stress conditions such as ischemia/reperfusion, cardiac hypertrophy and heart failure can trigger a substantial increase in autophagy.[179] Autophagy deficient mouse models show the accumulation of misfolded proteins and dysfunctional organelles and develop cardiac dysfunction. The mitochondria-specific form of autophagy is called mitophagy. Dysfunctional mitochondria are enclosed in a double membrane called phagophore, that eventually fuses with the lysosome membrane, releasing its content for degradation.[180] CL plays an important role in identifying dysfunctional mitochondria and targeting them for mitophagy. The unique biochemical properties of CL with two negative charges make CL a bona fide signaling receptor. Under stress conditions CL, is externalized and serves as a binding site for the recruitment of interaction partners, executing autophagy.

The accumulation of enlarged and dysfunctional mitochondria in BTHS indicates a defect in mitochondrial clearance by mitophagy. Studies in yeast deficient of CL biosynthesis have already suggested an involvement of CL in the execution of mitophagy.[181] Several aspects of mitophagy are found to be particularly dependent on CL. Due to the limited size of the phagophore, mitochondria need to be separated from their network by fission to be incorporated into phagophores. The CL-dependent fission protein GTPase Drp1 plays a critical role in generating mitochondrial fragments of appropriate size for turnover.[182] In macrophages, the immunity-related GTPase IRGM translocates from the cytosol to mitochondria, where it specifically interacts with CL and plays an essential role in mitochondrial fission upon mitophagy induction.[183] The activating factor Beclin 1 interacts with CL on the OM, indicating a role for CL in mitophagy induction.[184-186] Also the adaptor molecule LC3 and functionally similar adaptor molecules, which label mitochondria for their degradation by mitophagy, have a high affinity for CL.[187,188] Interestingly, a particular defect in the processing of LC3 was recently identified in a cell model of Barth syndrome.[189] Consistent with this, studies in tafazzin deficient cell models have revealed defective biogenesis of mitophagosomes.[190]

8 | THERAPEUTIC CONCEPTS IN BTHS

Gene therapy was tested using adeno-associated virus (AAV)-mediated tafazzin expression in the tafazzin knockdown mouse model.[191] Whereas global deletion of tafazzin caused embryonic and neonatal lethality, impaired growth, dilated cardiomyopathy, and skeletal myopathy, adenovirus mediated tafazzin expression rescued these phenotypes. Cardiomyocyte-specific inactivation of tafazzin caused progressive dilated cardiomyopathy, which was also prevented by the gene therapy approach.[191] Other approaches rescued the CL pool by blocking the CL phosholipase activity. Inhibiting CL remodeling by the CL phosholipase prevents CL conversion to MLCL.[46] Therefore, a fully acylated CL pool will be established, which differs from the mature pool in its acylation pattern.[46] This strategy was tested in a tafazzin deficient *Drosophila* strain, where it reverted a male sterility phenotype. Pharmacological inhibition of phospholipase A2 in patient lymphoblasts restored CL amounts in vitro.[46] However, genetic inactivation of iPLA2c in the tafazzin knockdown model did not prevent the decrease in tetralinoleyl CL. As iPLA2c belongs to a large family of phospholipases with yet unknown substrate specificities, these data indicate that iPLA2c is not involved in CL remodeling in the mammalian heart.

Pharmacological intervention targeting this protein family might also have severe side effects and affects other cellular processes, including the release of arachidonic acid, apoptosis, and store-operated Ca^{2+} entry.[192] In an alternative approach, deficient CL remodeling was counteracted by the administration of linoleic acid as a precursor molecule for CL biosynthesis. This approach reestablished CL levels in a dose dependent manner in fibroblasts from BTHS patients and rescued abnormalities in the sarcomeric structure in patient derived cardiomyocytes.[193]

The tetrapeptide Elamipretide (SS-31) accumulates in mitochondria based on its direct interaction with CL.[194] Elamipretide particularly prevents cytochrome c mediated ROS production. Under pathological stress, cytochrome c undergoes conformational changes, which induces a peroxidase-like activity causing large amounts of ROS emission. CL locates in close proximity of the active site of peroxidation and becomes itself a target of peroxidation. Oxidized forms of CL reduce their interaction with cytochrome c, allowing cytochrome c release during apoptosis.[195] Elamipretide potently inhibited CL-induced cytochrome *c* peroxidase activity. In animal models of ischemia/reperfusion, Elamipretide protected the structure of the mitochondrial cristae and reestablished energy metabolism.[194,195] However, in a phase II clinical trial (TAZPOWER trial, NCT0309879) on 12 BTHS patients, treatment with Elamipretide did not improve the 6-minute walking distance in patients. Although this argues against a causative role of mitochondrial ROS in BTHS pathology, larger clinical trials may reveal the long-term efficacy of Elamipretide in BTHS.

9 | OTHER CARDIAC DISEASES WITH CARDIOLIPIN DEFECTS

Diseases with a direct link to alterations in the CL pool, besides Barth syndrome, comprise of Sengers disease (OMIM 212350) and Dilated Cardiomyopathy with Ataxia (DCMA, OMIM 610198). DCMA is associated with ataxia, growth failure and dilated cardiomyopathy, left ventricular hypertrabeculation and QT interval prolongation.[196,197] DCMA is an autosomal recessive disease caused by mutations in the gene encoding DNAJC19. This protein shares sequence similarities with proteins of the mitochondrial protein import machinery of the IM, but a defect protein import was not reported.[196,198] DNAJC19 interacts with prohibitins, a family of scaffold proteins, required for the formation of lipid domains in the inner mitochondrial membrane. It was speculated that the role of this interaction is to promote the formation of a lipid environment, which is required for the enzymatic function of tafazzin in CL remodeling. This would explain significant changes in CL acylation pattern in cellular models of DCMA.[196]

Sengers syndrome is manifested as hypertrophic cardiomyopathy, congenital cataracts and 3-methylglutaconic aciduria, skeletal myopathy and lactic acidosis.[10,199-201] Mitochondrial morphology is abnormal in Sangers syndrome, and defects in mitochondrial respiration and in complexes I, III, IV, and V have been described. The causative mutation for Sengers syndrome is in the gene encoding the mitochondrial enzyme acylglycerolkinase (AGK), which catalyzes the phosphorylation of diacylglycerol (DAG) to form phosphodiacylglycerol, which serves as a precursor molecule for the biosynthesis of CL (see above). As AGK is also a component of the mitochondrial carrier translocase TIM22 and participates in protein import of mitochondrial carrier proteins,[202,203] it is unclear which of the two functions contribute mostly to the pathophysiology of the disease. Changes in CL levels are also involved in other cardiac modifications including ischemia/reperfusion injury, diabetic cardiomyopathy and the aging heart. Understanding the manifold functions of CL will help designing therapeutic strategies for BTHS, Sangers syndrome, DCMA and other cardiac diseases.

10 | CONCLUSIONS

Mitochondria are central hubs in cardiac metabolism and play essential roles in energy metabolism, redox homeostasis and ROS defense. Essential mitochondrial functions are associated with the inner (or outer) membrane. Many catalytic activities depend on the phospholipid CL, which plays a role in mitochondrial protein transport, shaping mitochondrial morphology, and is required for mitochondrial biogenesis. As an integral component of the respiratory chain, CL is directly involved in energy conversion and also Krebs cycle functions. CL is also important for the stability of the MCU, which controls Ca^{2+} influx and metabolic regulation. Defects in the biosynthesis and remodeling of CL affects particularly tissues with high-energy metabolism, such as the heart and skeletal muscle. The treatment of diseases with CL defects is an unmet clinical need and therefore, understanding the complex alterations that arise from CL defects is a key step to develop efficient strategies to eventually improve or even heal Barth syndrome or its related diseases.

ACKNOWLEDGMENTS

C. M. was and is supported by the German Heart Foundation (Margret Elisabeth Strauß-Projektförderung), the

Barth Syndrome Foundation, the German Research Foundation (DFG; Ma 2528/7-1, SFB 894, TRR-219) and the German Federal Agency for Education and Research (BMBF; 01EO1504). J. D. is supported by the DFG (DU1839/2-1), the BMBF and the Barth Syndrome Foundation. Open access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTEREST

C. M. received honoraria as a speaker or advisor from Stealth Biotherapeutics, but not in the past 5 years. J. D. declares that he has no conflict of interest.

INFORMED CONSENT AND ANIMAL RIGHTS

This article does not contain any studies with human or animal subjects performed by the any of the authors.

AUTHOR CONTRIBUTIONS

Jan Dudek has drafted the manuscript and designed the figures Christoph Maack was involved in writing and proofreading the manuscript.

REFERENCES

1. Lopaschuk GD, Karwi QG, Tian R, Wende AR, Abel ED. Cardiac energy metabolism in heart failure. *Circ Res*. 2021;128:1487-1513.
2. Bertero E, Maack C. Metabolic remodelling in heart failure. *Nat Rev Cardiol*. 2018;15:457-470.
3. Copeland DE, Dalton AJ. An association between mitochondria and the endoplasmic reticulum in cells of the pseudobranch gland of a teleost. *J Biophys Biochem Cytol*. 1959;5:393-396.
4. Elbaz-Alon Y, Rosenfeld-Gur E, Shinder V, Futerman AH, Geiger T, Schuldiner M. A dynamic Interface between vacuoles and mitochondria in yeast. *Dev Cell*. 2014;30:95-102.
5. Tatsuta T, Scharwey M, Langer T. Mitochondrial lipid trafficking. *Trends Cell Biol*. 2014;24:44-52.
6. Horvath SE, Daum G. Lipids of mitochondria. *Prog Lipid Res*. 2013;52:590-614.
7. Li J, Romestaing C, Han X, et al. Cardiolipin remodeling by ALCAT1 links oxidative stress and mitochondrial dysfunction to obesity. *Cell Metab*. 2010;12:154-165.
8. Mulligan CM, Le CH, Demooy AB, Nelson CB, Chicco AJ. Inhibition of delta-6 desaturase reverses cardiolipin remodeling and prevents contractile dysfunction in the aged mouse heart without altering mitochondrial respiratory function. *J Gerontol A Biol Sci Med Sci*. 2014;69:799-809.
9. Paradies G, Petrosillo G, Pistolese M, Di Venosa N, Serena D, Ruggiero FM. Lipid peroxidation and alterations to oxidative metabolism in mitochondria isolated from rat heart subjected to ischemia and reperfusion. *Free Radic Biol Med*. 1999;27:42-50.
10. Sengers RC, Trijbels JM, Willems JL, Daniels O, Stadhouders AM. Congenital cataract and mitochondrial myopathy of skeletal and heart muscle associated with lactic acidosis after exercise. *J Pediatr*. 1975;86:873-880.
11. Sparkes R, Patton D, Bernier F. Cardiac features of a novel autosomal recessive dilated cardiomyopathic syndrome due to defective importation of mitochondrial protein. *Cardiol Young*. 2007;17:215-217.
12. Bione S, D'Adamo P, Maestrini E, Gedeon A, Bolhuis P, Toniolo D. A novel X-linked gene, G4.5. Is responsible for Barth syndrome. *Nat Genet*. 1996;12:385-389.
13. Johnston J, Kelley RI, Feigenbaum A, et al. Mutation characterization and genotype-phenotype correlation in Barth syndrome. *Am J Hum Genet*. 1997;61:1053-1058.
14. Kang S-L, Forsey J, Dudley D, Steward CG, Tsai-Goodman B. Clinical characteristics and outcomes of cardiomyopathy in Barth syndrome: the UK experience. *Pediatr Cardiol*. 2016;37:167-176.
15. Roberts AE, Nixon C, Steward CG, et al. The Barth syndrome registry: distinguishing disease characteristics and growth data from a longitudinal study. *Am J Med Genet A*. 2012;158A:2726-2732.
16. Spencer CT, Bryant RM, Day J, et al. Cardiac and clinical phenotype in Barth syndrome. *Pediatrics*. 2006;118:e337-e346.
17. Spencer CT, Byrne BJ, Bryant RM, et al. Impaired cardiac reserve and severely diminished skeletal muscle O_2 utilization mediate exercise intolerance in Barth syndrome. *Am J Physiol Heart Circ Physiol*. 2011;301:H2122-H2129.
18. Spencer CT, Byrne BJ, Gewitz MH, et al. Ventricular arrhythmia in the X-linked cardiomyopathy Barth syndrome. *Pediatr Cardiol*. 2005;26:632-637.
19. Hornby B, McClellan R, Buckley L, Carson K, Gooding T, Vernon HJ. Functional exercise capacity, strength, balance and motion reaction time in Barth syndrome. *Orphanet J Rare Dis*. 2019;14:37.
20. Cade WT, Bohnert KL, Peterson LR, et al. Blunted fat oxidation upon submaximal exercise is partially compensated by enhanced glucose metabolism in children, adolescents, and young adults with Barth syndrome. *J Inherit Metab Dis*. 2019;42:480-493.
21. Barth P, Scholte H, Berden J, et al. An X-linked mitochondrial disease affecting cardiac muscle, skeletal muscle and neutrophil leucocytes. *J Neurol Sci*. 1983;62:327-355.
22. Corrado M, Edwards-Hicks J, Villa M, et al. Dynamic cardiolipin synthesis is required for CD8(+) T cell immunity. *Cell Metab*. 2020;32:981-995.e987.
23. Kuijpers TW, Maianski NA, Tool ATJ, et al. Neutrophils in Barth syndrome (BTHS) avidly bind annexin-V in the absence of apoptosis. *Blood*. 2004;103:3915-3923.
24. Clarke SLN, Bowron A, Gonzalez IL, et al. Barth syndrome. *Orphanet J Rare Dis*. 2013;8:23.
25. Schmidt MR, Birkebaek N, Gonzalez I, Sunde L. Barth syndrome without 3-methylglutaconic aciduria. *Acta Paediatr*. 2004;93:419-421.
26. Cade WT, Bohnert KL, Bittel AJ, et al. Arginine kinetics are altered in a pilot sample of adolescents and young adults with Barth syndrome. *Mol Genet Metab Rep*. 2020;25:100675.
27. Sandlers Y, Mercier K, Pathmasiri W, et al. Metabolomics reveals new mechanisms for pathogenesis in Barth syndrome and introduces novel roles for cardiolipin in cellular function. *PLoS ONE*. 2016;11:e0151802.

28. Vernon HJ, Sandlers Y, McClellan R, Kelley RI. Clinical laboratory studies in Barth syndrome. *Mol Genet Metab*. 2014;112:143-147.
29. Zegallai HM, Hatch GM. Barth syndrome: cardiolipin, cellular pathophysiology, management, and novel therapeutic targets. *Mol Cell Biochem*. 2021;476:1605-1629.
30. Raja V, Joshi AS, Li G, Maddipati KR, Greenberg ML. Loss of cardiolipin leads to perturbation of acetyl-CoA synthesis. *J Biol Chem*. 2017;292:1092-1102.
31. Osman C, Voelker DR, Langer T. Making heads or tails of phospholipids in mitochondria. *J Cell Biol*. 2011;192:7-16.
32. Tamura Y, Endo T, Iijima M, Sesaki H. Ups1p and Ups2p antagonistically regulate cardiolipin metabolism in mitochondria. *J Cell Biol*. 2009;185:1029-1045.
33. Vukotic M, Nolte H, Konig T, et al. Acylglycerol kinase mutated in Sengers syndrome is a subunit of the TIM22 protein translocase in mitochondria. *Mol Cell*. 2017;67:471-483.e477.
34. Waggoner DW, Johnson LB, Mann PC, Morris V, Guastella J, Bajjalieh SM. MuLK, a eukaryotic multi-substrate lipid kinase. *J Biol Chem*. 2004;279:38228-38235.
35. Jiao H, Yin Y, Liu Z. Structures of the mitochondrial CDP-DAG synthase Tam41 suggest a potential lipid substrate pathway from membrane to the active site. *Structure (Lond, Engl: 1993)*. 2019;27:1258-1269.e1254.
36. He Q, Greenberg ML. Post-translational regulation of phosphatidylglycerolphosphate synthase in response to inositol. *Mol Microbiol*. 2004;53:1243-1249.
37. Xiao J, Engel JL, Zhang J, Chen MJ, Manning G, Dixon JE. Structural and functional analysis of PTPMT1, a phosphatase required for cardiolipin synthesis. 2011;108:11860-11865.
38. Zhong Q, Greenberg ML. Regulation of phosphatidylglycerophosphate synthase by inositol in *Saccharomyces cerevisiae* is not at the level of PGS1 mRNA abundance. *J Biol Chem*. 2003;278:33978-33984.
39. Bao MH, Yang C, Tse AP, et al. Genome-wide CRISPR-Cas9 knockout library screening identified PTPMT1 in cardiolipin synthesis is crucial to survival in hypoxia in liver cancer. *Cell Rep*. 2021;34:108676.
40. Chang SC, Heacock PN, Mileykovskaya E, Voelker DR, Dowhan W. Isolation and characterization of the gene (CLS1) encoding cardiolipin synthase in *Saccharomyces cerevisiae*. *J Biol Chem*. 1998;273:14933-14941.
41. Chen D, Zhang X-Y, Shi Y. Identification and functional characterization of hCLS1, a human cardiolipin synthase localized in mitochondria. *Biochem J*. 2006;398:169-176.
42. Hostetler KY. Effect of thyroxine on the activity of mitochondrial cardiolipin synthase in rat liver. *Biochim Biophys Acta (BBA)—Lipids Lipid Metab*. 1991;1086:139-140.
43. Boynton TOH, Shimkets LJ. Myxococcus CsgA, Drosophila sniffer, and human HSD10 are cardiolipin phospholipases. *Genes Dev*. 2015;29:1903-1914.
44. Cao J, Liu Y, Lockwood J, Burn P, Shi Y. A novel cardiolipin-remodeling pathway revealed by a gene encoding an endoplasmic reticulum-associated acyl-CoA:lysocardiolipin acyltransferase (ALCAT1) in mouse. *J Biol Chem*. 2004;279:31727-31734.
45. Li M, Zhong Z, Zhu J, et al. Identification and characterization of mitochondrial targeting sequence of human apurinic/apyrimidinic endonuclease 1. *J Biol Chem*. 2010;285:14871-14881.
46. Malhotra A, Edelman-Novemsky I, Xu Y, et al. Role of calcium-independent phospholipase A2 in the pathogenesis of Barth syndrome. *Proc Natl Acad Sci U S A*. 2009;106:2337-2341.
47. Mancuso DJ, Sims HF, Han X, et al. Genetic ablation of calcium-independent phospholipase A2gamma leads to alterations in mitochondrial lipid metabolism and function resulting in a deficient mitochondrial bioenergetic phenotype. *J Biol Chem*. 2007;282:34611-34622.
48. Xu Y, Malhotra A, Ren M, Schlame M. The enzymatic function of tafazzin. *J Biol Chem*. 2006;281:39217-39224.
49. Houtkooper RH, Rodenburg RJ, Thiels C, et al. Cardiolipin and monolysocardiolipin analysis in fibroblasts, lymphocytes, and tissues using high-performance liquid chromatography-mass spectrometry as a diagnostic test for Barth syndrome. *Anal Biochem*. 2009;387:230-237.
50. Kulik W, van Lenthe H, Stet FS, et al. Bloodspot assay using HPLC-tandem mass spectrometry for detection of Barth syndrome. *Clin Chem*. 2008;54:371-378.
51. Mejia EM, Zegallai H, Bouchard ED, Banerji V, Ravandi A, Hatch GM. Expression of human monolysocardiolipin acyltransferase-1 improves mitochondrial function in Barth syndrome lymphoblasts. *J Biol Chem*. 2018;293:7564-7577.
52. Landriscina C, Megli FM, Quagliariello E. Turnover of fatty acids in rat liver cardiolipin: comparison with other mitochondrial phospholipids. *Lipids*. 1976;11:61-66.
53. Wahjudi PN, Yee JK, Martinez SR, et al. Turnover of nonessential fatty acids in cardiolipin from the rat heart. *J Lipid Res*. 2011;52:2226-2233.
54. Xu Y, Schlame M. The turnover of glycerol and acyl moieties of cardiolipin. *Chem Phys Lipids*. 2014;179:17-24.
55. Xu Y, Phoon CKL, Berno B, D'Souza K, Hoedt E. Loss of protein association causes cardiolipin degradation in Barth syndrome. *Nat Chem*. 2016;12(8):641-647.
56. Buckland AG, Kinkaid AR, Wilton DC. Cardiolipin hydrolysis by human phospholipases A2: the multiple enzymatic activities of human cytosolic phospholipase A2. *Biochim Biophys Acta (BBA)—Lipids Lipid Metab*. 1998;1390:65-72.
57. Ghosh M, Loper R, Gelb MH, Leslie CC. Identification of the expressed form of human cytosolic phospholipase A2beta (cPLA2beta): cPLA2beta3 is a novel variant localized to mitochondria and early endosomes. *J Biol Chem*. 2006;281:16615-16624.
58. Huang H, Gao Q, Peng X, et al. piRNA-associated germline nuage formation and spermatogenesis require MitoPLD profusogenic mitochondrial-surface lipid signaling. *Dev Cell*. 2011;20:376-387.
59. Watanabe Y, Tamura Y, Kawano S, Endo T. Structural and mechanistic insights into phospholipid transfer by Ups1-Mdm35 in mitochondria. *Nat Commun*. 2015;6:7922.
60. Connerth M, Tatsuta T, Haag M, Klecker T, Westermann B, Langer T. Intramitochondrial transport of phosphatidic acid in yeast by a lipid transfer protein. *Science*. 2012;338:815-818.
61. Gebert N, Joshi AS, Kutik S, et al. Mitochondrial cardiolipin involved in outer-membrane protein biogenesis: implications for Barth syndrome. *Curr Biol*. 2009;19:2133-2139.

62. Oemer G, Koch J, Wohlfarter Y, et al. Phospholipid acyl chain diversity controls the tissue-specific assembly of mitochondrial cardiolipins. *Cell Rep*. 2020;30:4281.
63. Stanley WC, Khairallah RJ, Dabkowski ER. Update on lipids and mitochondrial function: impact of dietary n-3 polyunsaturated fatty acids. *Curr Opin Clin Nutr Metab Care*. 2012;15:122-126.
64. Schlame M, Acehan D, Berno B, et al. The physical state of lipid substrates provides transacylation specificity for tafazzin. *Nat Chem Biol*. 2012;8:862-869.
65. Xu Y, Anjaneyulu M, Donelian A, et al. Assembly of the complexes of oxidative phosphorylation triggers the remodeling of cardiolipin. *Proc Natl Acad Sci U S A*. 2019;116:11235-11240.
66. Seneviratne AK, Xu M, Aristizabal Henao JJ, et al. The mitochondrial transacylase, tafazzin, regulates AML stemness by modulating intracellular levels of phospholipids. *Cell Stem Cell*. 2019;24:1007.
67. Kiebish MA, Yang K, Liu X, et al. Dysfunctional cardiac mitochondrial bioenergetic, lipidomic, and signaling in a murine model of Barth syndrome. *J Lipid Res*. 2013;54:1312-1325.
68. Kimura T, Kimura AK, Ren M, et al. Plasmalogen loss caused by remodeling deficiency in mitochondria. *Life Sci Alliance*. 2019;2:e201900348.
69. Sindelar PJ, Guan Z, Dallner G, Ernster L. The protective role of plasmalogens in iron-induced lipid peroxidation. *Free Radic Biol Med*. 1999;26:318-324.
70. Le C, Gong Q, Stice JP, Knowlton AA. Mitochondrial OPA1, apoptosis and heart failure. *Cardiovasc Res*. 2009;84:91-99.
71. Sharov VG, Sabbah HN, Shimoyama H, Goussev AV, Lesch M, Goldstein S. Evidence of cardiocyte apoptosis in myocardium of dogs with chronic heart failure. *Am J Pathol*. 1996;148:141-149.
72. Montaigne D, Marechal X, Coisne A, et al. Myocardial contractile dysfunction is associated with impaired mitochondrial function and dynamics in type 2 diabetic but not in obese patients. *Circulation*. 2014;130:554-564.
73. Kalkhoran SB, Kriston-Vizi J, Hernandez-Resendiz S, et al. Hydralazine protects the heart against acute ischemia/reperfusion injury by inhibiting Drp1-mediated mitochondrial fission. *Cardiovasc Res*. 2021. https://doi.org/10.1093/cvr/cvaa343. Published online ahead of print.
74. Sharp WW, Fang YH, Han M, et al. Dynamin-related protein 1 (Drp1)-mediated diastolic dysfunction in myocardial ischemia-reperfusion injury: therapeutic benefits of Drp1 inhibition to reduce mitochondrial fission. *FASEB J*. 2014;28:316-326.
75. Kim H, Scimia MC, Wilkinson D, et al. Fine-tuning of Drp1/Fis1 availability by AKAP121/Siah2 regulates mitochondrial adaptation to hypoxia. *Mol Cell*. 2011;44:532-544.
76. Bouche L, Kamel R, Tamareille S, et al. DRP1 haploinsufficiency attenuates cardiac ischemia/reperfusion injuries. *PLoS ONE*. 2021;16:e0248554.
77. Brady NR, Hamacher-Brady A, Gottlieb RA. Proapoptotic BCL-2 family members and mitochondrial dysfunction during ischemia/reperfusion injury, a study employing cardiac HL-1 cells and GFP biosensors. *Biochim Biophys Acta*. 2006;1757:667-678.
78. Acehan D, Vaz F, Houtkooper RH, et al. Cardiac and skeletal muscle defects in a mouse model of human Barth syndrome. *J Biol Chem*. 2011;286:899-908.
79. Acehan D, Xu Y, Stokes DL, Schlame M. Comparison of lymphoblast mitochondria from normal subjects and patients with Barth syndrome using electron microscopic tomography. *Lab Invest*. 2007;87:40-48.
80. Gonzalvez F, D'Aurelio M, Boutant M, et al. Barth syndrome: cellular compensation of mitochondrial dysfunction and apoptosis inhibition due to changes in cardiolipin remodeling linked to tafazzin (TAZ) gene mutation. *Biochim Biophys Acta*. 2013;1832:1194-1206.
81. Frohman MA. Role of mitochondrial lipids in guiding fission and fusion. *J Mol Med (Berl)*. 2015;93:263-269.
82. Eisner V, Cupo RR, Gao E, et al. Mitochondrial fusion dynamics is robust in the heart and depends on calcium oscillations and contractile activity. *Proc Natl Acad Sci U S A*. 2017;114:E859-E868.
83. Gong G, Song M, Csordas G, Kelly DP, Matkovich SJ, Dorn GW. Parkin-mediated mitophagy directs perinatal cardiac metabolic maturation in mice. *Science*. 2015;350:aad2459.
84. Giacomello M, Pyakurel A, Glytsou C, Scorrano L. The cell biology of mitochondrial membrane dynamics. *Nat Rev Mol Cell Biol*. 2020;21:204-224.
85. Choi S-Y, Huang P, Jenkins GM, Chan DC, Schiller J, Frohman MA. A common lipid links Mfn-mediated mitochondrial fusion and SNARE-regulated exocytosis. *Nat Cell Biol*. 2006;8:1255-1262.
86. Baba T, Kashiwagi Y, Arimitsu N, et al. Phosphatidic acid (PA)-preferring phospholipase A1 regulates mitochondrial dynamics. *J Biol Chem*. 2014;289:11497-11511.
87. Zorzano A, Liesa M, Sebastian D, Segales J, Palacin M. Mitochondrial fusion proteins: dual regulators of morphology and metabolism. *Semin Cell Dev Biol*. 2010;21:566-574.
88. Del Dotto V, Fogazza M, Carelli V, Rugolo M, Zanna C. Eight human OPA1 isoforms, long and short: what are they for? *Biochim Biophys Acta Bioenerg*. 2018;1859:263-269.
89. Wai T, García-Prieto J, Baker MJ, et al. Imbalanced OPA1 processing and mitochondrial fragmentation cause heart failure in mice. *Science*. 2015;350:aad0116.
90. Ban T, Ishihara T, Kohno H, et al. Molecular basis of selective mitochondrial fusion by heterotypic action between OPA1 and cardiolipin. *Nat Cell Biol*. 2017;505:335.
91. DeVay RM, Dominguez-Ramirez L, Lackner LL, Hoppins S, Stahlberg H, Nunnari J. Coassembly of Mgm1 isoforms requires cardiolipin and mediates mitochondrial inner membrane fusion. *J Cell Biol*. 2009;186:793-803.
92. Meglei G, McQuibban GA. The dynamin-related protein Mgm1p assembles into oligomers and hydrolyzes GTP to function in mitochondrial membrane fusion. *Biochemistry*. 2009;48:1774-1784.
93. Richter V, Palmer CS, Osellame LD, et al. Structural and functional analysis of MiD51, a dynamin receptor required for mitochondrial fission. *J Cell Biol*. 2014;204:477-486.
94. Francy CA, Clinton RW, Frohlich C, Murphy C, Mears JA. Cryo-EM studies of Drp1 reveal cardiolipin interactions that activate the helical oligomer. *Sci Rep*. 2017;7:10744.
95. Frohlich C, Grabiger S, Schwefel D, et al. Structural insights into oligomerization and mitochondrial remodelling of dynamin 1-like protein. *EMBO J*. 2013;32:1280-1292.

96. Strack S, Cribbs JT. Allosteric modulation of Drp1 mechanoenzyme assembly and mitochondrial fission by the variable domain. *J Biol Chem*. 2012;287:10990-11001.
97. Sabbah HN, Gupta RC, Singh-Gupta V, Zhang K, Lanfear DE. Abnormalities of mitochondrial dynamics in the failing heart: normalization following Long-term therapy with elamipretide. *Cardiovasc Drugs Ther*. 2018;32:319-328.
98. Fernandez-Mosquera L, Diogo CV, Yambire KF, et al. Acute and chronic mitochondrial respiratory chain deficiency differentially regulate lysosomal biogenesis. *Sci Rep*. 2017;7:45076.
99. Fernandez-Mosquera L, Yambire KF, Couto R, et al. Mitochondrial respiratory chain deficiency inhibits lysosomal hydrolysis. *Autophagy*. 2019;15:1572-1591.
100. Yambire KF, Fernandez-Mosquera L, Steinfeld R, et al. Mitochondrial biogenesis is transcriptionally repressed in lysosomal lipid storage diseases. *Elife*. 2019;8:e39598. https://doi.org/10.7554/eLife.39598
101. Mohanty A, McBride HM. Emerging roles of mitochondria in the evolution, biogenesis, and function of peroxisomes. *Front Physiol*. 2013;4:268.
102. Schrader M, Costello J, Godinho LF, Islinger M. Peroxisome-mitochondria interplay and disease. *J Inherit Metab Dis*. 2015;38:681-702.
103. Giacomello M, Pellegrini L. The coming of age of the mitochondria-ER contact: a matter of thickness. *Cell Death Differ*. 2016;23:1417-1427.
104. de Brito OM, Scorrano L. Mitofusin 2 tethers endoplasmic reticulum to mitochondria. *Nature*. 2008;456:605-610.
105. Chen Y, Csordas G, Jowdy C, et al. Mitofusin 2-containing mitochondrial-reticular microdomains direct rapid cardiomyocyte bioenergetic responses via Interorganelle Ca^{2+} CrosstalkNovelty and significance. *Circ Res*. 2012;111:863-875.
106. Wu S, Lu Q, Wang Q, et al. Binding of FUN14 domain containing 1 with inositol 1,4,5-trisphosphate receptor in mitochondria-associated endoplasmic reticulum membranes maintains mitochondrial dynamics and function in hearts in vivo. *Circulation*. 2017;136:2248-2266.
107. Wolf DM, Segawa M, Kondadi AK, et al. Individual cristae within the same mitochondrion display different membrane potentials and are functionally independent. *EMBO J*. 2019;38:e101056.
108. Kondadi AK, Anand R, Hansch S, et al. Cristae undergo continuous cycles of membrane remodelling in a MICOS-dependent manner. *EMBO Rep*. 2020;21:e49776.
109. Rampelt H, Wollweber F, Gerke C, et al. Assembly of the mitochondrial cristae organizer Mic10 is regulated by Mic26-Mic27 antagonism and cardiolipin. *J Mol Biol*. 2018;430:1883-1890.
110. Friedman JR, Mourier A, Yamada J, McCaffery JM, Nunnari J, Youle RJ. MICOS coordinates with respiratory complexes and lipids to establish mitochondrial inner membrane architecture. *Elife*. 2015;4:e07739.
111. Weber TA, Koob S, Heide H, et al. APOOL is a cardiolipin-binding constituent of the mitofilin/MINOS protein complex determining cristae morphology in mammalian mitochondria. *PLoS ONE*. 2013;8:e63683.
112. Anand R, Kondadi AK, Meisterknecht J, et al. MIC26 and MIC27 cooperate to regulate cardiolipin levels and the landscape of OXPHOS complexes. *Life Sci Alliance*. 2020;3:e202000711.
113. Chatzispyrou IA, Guerrero-Castillo S, Held NM, et al. Barth syndrome cells display widespread remodeling of mitochondrial complexes without affecting metabolic flux distribution. *Biochim Biophys Acta Mol Basis Dis*. 2018;1864:3650-3658.
114. Ernst R, Ballweg S, Levental I. Cellular mechanisms of physicochemical membrane homeostasis. *Curr Opin Cell Biol*. 2018;53:44-51.
115. Harayama T, Riezman H. Understanding the diversity of membrane lipid composition. *Nat Rev Mol Cell Biol*. 2018;19:281-296.
116. Fiedorczuk K, Letts JA, Degliesposti G, Kaszuba K, Skehel M, Sazanov LA. Atomic structure of the entire mammalian mitochondrial complex I. *Nature*. 2016;538:406-410.
117. Lange C, Nett JH, Trumpower BL, Hunte C. Specific roles of protein-phospholipid interactions in the yeast cytochrome bc1 complex structure. *EMBO J*. 2001;20:6591-6600.
118. Palsdottir H, Lojero CG, Trumpower BL, Hunte C. Structure of the yeast cytochrome bc1 complex with a hydroxyquinone anion Qo site inhibitor bound. *J Biol Chem*. 2003;278:31303-31311.
119. Itoh KS, Aoyama H, Muramoto K, et al. Structures and physiological roles of 13 integral lipids of bovine heart cytochrome c oxidase. *EMBO J*. 2007;26:1713-1725.
120. Duncan AL, Robinson AJ, Walker JE. Cardiolipin binds selectively but transiently to conserved lysine residues in the rotor of metazoan ATP synthases. 2016;113:8687-8692.
121. Eble KS, Coleman WB, Hantgan RR, Cunningham CC. Tightly associated cardiolipin in the bovine heart mitochondrial ATP synthase as analyzed by 31P nuclear magnetic resonance spectroscopy. *J Biol Chem*. 1990;265:19434-19440.
122. Morelli AM, Ravera S, Calzia D, Panfoli I. Hypothesis of lipid-phase-continuity proton transfer for aerobic ATP synthesis. *J Cereb Blood Flow Metab*. 2013;33:1838-1842.
123. Brandner K, Mick DU, Frazier AE, Taylor RD, Meisinger C, Rehling P. Taz1, an outer mitochondrial membrane protein, affects stability and assembly of inner membrane protein complexes: implications for Barth syndrome. *Mol Biol Cell*. 2005;16:5202-5214.
124. Letts JA, Fiedorczuk K, Sazanov LA. The architecture of respiratory supercomplexes. *Nature*. 2016;537:644-648.
125. McKenzie M, Lazarou M, Thorburn DR, Ryan MT. Mitochondrial respiratory chain supercomplexes are destabilized in Barth syndrome patients. *J Mol Biol*. 2006;361:462-469.
126. Wu M, Gu J, Guo R, Huang Y, Yang M. Structure of mammalian respiratory supercomplex I1III2IV1. *Cell*. 2016;167:1598-1609.e1510.
127. Bazan S, Mileykovskaya E, Mallampalli VKPS, Heacock P, Sparagna GC, Dowhan W. Cardiolipin-dependent reconstitution of respiratory supercomplexes from purified *Saccharomyces cerevisiae* complexes III and IV. 2013;288:401-411.
128. Mileykovskaya E, Penczek PA, Fang J, Mallampalli VKPS, Sparagna GC, Dowhan W. Arrangement of the respiratory chain complexes in *Saccharomyces cerevisiae* supercomplex III2IV2 revealed by single particle cryo-electron microscopy. *J Biol Chem*. 2012;287:23095-23103.

129. Pfeiffer K, Gohil V, Stuart R, et al. Cardiolipin stabilizes respiratory chain supercomplexes. *J Biol Chem*. 2003;278:52873-52880.
130. Zhang M, Mileykovskaya E, Dowhan W. Cardiolipin is essential for organization of complexes III and IV into a supercomplex in intact yeast mitochondria. *J Biol Chem*. 2005;280:29403-29408.
131. Dudek J, Cheng IF, Balleininger M, et al. Cardiolipin deficiency affects respiratory chain function and organization in an induced pluripotent stem cell model of Barth syndrome. *Stem Cell Res*. 2013;11:806-819.
132. Dudek J, Cheng IF, Chowdhury A, et al. Cardiac-specific succinate dehydrogenase deficiency in Barth syndrome. *EMBO Mol Med*. 2015;8:139-154.
133. Huang Y, Powers C, Madala SK, et al. Cardiac metabolic pathways affected in the mouse model of Barth syndrome. *PLoS ONE*. 2015;10:e0128561.
134. Maas E, Bisswanger H. Localization of the alpha-oxoacid dehydrogenase multienzyme complexes within the mitochondrion. *FEBS Lett*. 1990;277:189-190.
135. Li Y, Lou W, Raja V, et al. Cardiolipin-induced activation of pyruvate dehydrogenase links mitochondrial lipid biosynthesis to TCA cycle function. *J Biol Chem*. 2019;294:11568-11578.
136. Fatica EM, DeLeonibus GA, House A, et al. Barth syndrome: exploring cardiac metabolism with induced pluripotent stem cell-derived cardiomyocytes. *Metabolites*. 2019;9(12):1-22. https://doi.org/10.3390/metabo9120306
137. Beyer K, Klingenberg M. ADP/ATP carrier protein from beef heart mitochondria has high amounts of tightly bound cardiolipin, as revealed by 31P nuclear magnetic resonance. *Biochemistry*. 1985;24:3821-3826.
138. Pebay-Peyroula E, Dahout-Gonzalez C, Kahn R, Trézéguet V, Lauquin GJM, Brandolin G. Structure of mitochondrial ADP/-ATP carrier in complex with carboxyatractyloside. *Nature*. 2003;426:39-44.
139. Senoo N, Kandasamy S, Ogunbona OB, Baile MG, Lu Y, Claypool SM. Cardiolipin, conformation, and respiratory complex-dependent oligomerization of the major mitochondrial ADP/ATP carrier in yeast. *Sci Adv*. 2020;6:eabb0780.
140. Indiveri C, Tonazzi A, Prezioso G, Palmieri F. Kinetic characterization of the reconstituted carnitine carrier from rat liver mitochondria. *Biochim Biophys Acta*. 1991;1065:231-238.
141. Kaplan RS, Mayor JA, Johnston N, Oliveira DL. Purification and characterization of the reconstitutively active tricarboxylate transporter from rat liver mitochondria. *J Biol Chem*. 1990;265:13379-13385.
142. Palmieri F, Bisaccia F, Capobianco L, Iacobazzi V, Indiveri C, Zara V. Structural and functional properties of mitochondrial anion carriers. *Biochim Biophys Acta*. 1990;1018:147-150.
143. Chen S, He Q, Greenberg ML. Loss of tafazzin in yeast leads to increased oxidative stress during respiratory growth. *Mol Microbiol*. 2008;68:1061-1072.
144. Wang G, McCain ML, Yang L, et al. Modeling the mitochondrial cardiomyopathy of Barth syndrome with induced pluripotent stem cell and heart-on-chip technologies. *Nat Med*. 2014;20:616-623.
145. He Q, Harris N, Ren J, Han X. Mitochondria-targeted antioxidant prevents cardiac dysfunction induced by tafazzin gene knockdown in cardiac myocytes. *Oxid Med Cell Longev*. 2014;2014:654198.
146. Johnson JM, Ferrara PJ, Verkerke ARP, et al. Targeted overexpression of catalase to mitochondria does not prevent cardioskeletal myopathy in Barth syndrome. *J Mol Cell Cardiol*. 2018;121:94-102.
147. Goncalves RLS, Schlame M, Bartelt A, Brand MD, Hotamisligil GS. Cardiolipin deficiency in Barth syndrome is not associated with increased superoxide/H_2O_2 production in heart and skeletal muscle mitochondria. *FEBS Lett*. 2020;595(3):415-432.
148. Chowdhury A, Aich A, Jain G, et al. Defective mitochondrial cardiolipin remodeling dampens HIF-1alpha expression in hypoxia. *Cell Rep*. 2018;25:561-570.e566.
149. Murphy MP. How mitochondria produce reactive oxygen species. *Biochem J*. 2009;417:1-13.
150. Turrens JF. Mitochondrial formation of reactive oxygen species. *J Physiol*. 2003;552:335-344.
151. Aon MA, Stanley BA, Sivakumaran V, et al. Glutathione/thioredoxin systems modulate mitochondrial H_2O_2 emission: an experimental-computational study. *J Gen Physiol*. 2012;139:479-491.
152. Ying W. NAD+/NADH and NADP+/NADPH in cellular functions and cell death: regulation and biological consequences. *Antioxid Redox Signal*. 2008;10:179-206.
153. Aon MA, Cortassa S, O'Rourke B. Redox-optimized ROS balance: a unifying hypothesis. *Biochim Biophys Acta*. 2010;1797:865-877.
154. Balaban RS, Nemoto S, Finkel T. Mitochondria, oxidants, and aging. *Cell*. 2005;120:483-495.
155. Bers DM. Altered cardiac myocyte Ca regulation in heart failure. *Physiology (Bethesda)*. 2006;21:380-387.
156. Lokuta AJ, Maertz NA, Meethal SV, et al. Increased nitration of sarcoplasmic reticulum Ca^{2+}-ATPase in human heart failure. *Circulation*. 2005;111:988-995.
157. Periasamy M, Janssen PM. Molecular basis of diastolic dysfunction. *Heart Fail Clin*. 2008;4:13-21.
158. Liu X, Wang S, Guo X, et al. Increased reactive oxygen species-mediated Ca(2+)/calmodulin-dependent protein kinase II activation contributes to calcium handling abnormalities and impaired contraction in Barth syndrome. *Circulation*. 2021;143:1894-1911.
159. Kohlhaas M, Maack C. Calcium release microdomains and mitochondria. *Cardiovasc Res*. 2013;98:259-268.
160. Dorn GW, Maack C. SR and mitochondria: calcium cross-talk between kissing cousins. *J Mol Cell Cardiol*. 2013;55:42-49.
161. Nickel AG, von Hardenberg A, Hohl M, et al. Reversal of mitochondrial transhydrogenase causes oxidative stress in heart failure. *Cell Metab*. 2015;22:472-484.
162. Szabadkai G, Simoni AM, Chami M, Wieckowski MR, Youle RJ, Rizzuto R. Drp-1-dependent division of the mitochondrial network blocks Intraorganellar Ca^{2+} waves and protects against Ca^{2+}-mediated apoptosis. *Mol Cell*. 2004;16:59-68.
163. Baughman JM, Perocchi F, Girgis HS, et al. Integrative genomics identifies MCU as an essential component of the mitochondrial calcium uniporter. *Nature*. 2011;476:341-345.

164. Oxenoid K, Dong Y, Cao C, et al. Architecture of the mitochondrial calcium uniporter. *Nature*. 2016;533:269-273.
165. Perocchi F, Gohil VM, Girgis HS, et al. MICU1 encodes a mitochondrial EF hand protein required for Ca(2+) uptake. *Nature*. 2010;467:291-296.
166. Raffaello A, De Stefani D, Sabbadin D, et al. The mitochondrial calcium uniporter is a multimer that can include a dominant-negative pore-forming subunit. *EMBO J*. 2013;32:2362-2376.
167. Sancak Y, Markhard AL, Kitami T, et al. EMRE is an essential component of the mitochondrial calcium uniporter complex. *Science*. 2013;342:1379-1382.
168. Phillips CB, Tsai CW, Tsai MF. The conserved aspartate ring of MCU mediates MICU1 binding and regulation in the mitochondrial calcium uniporter complex. *Elife*. 2019;8:e41112. https://orcid.org/0000-0001-5510-9554
169. Baradaran R, Wang C, Siliciano AF, Long SB. Cryo-EM structures of fungal and metazoan mitochondrial calcium uniporters. *Nature*. 2018;559:580-584.
170. Zhuo W, Zhou H, Guo R, et al. Structure of intact human MCU supercomplex with the auxiliary MICU subunits. *Protein Cell*. 2020;12(3):220-229.
171. Ghosh S, Basu Ball W, Madaris TR, et al. An essential role for cardiolipin in the stability and function of the mitochondrial calcium uniporter. *Proc Natl Acad Sci U S A*. 2020;117:16383-16390.
172. Kamer KJ, Grabarek Z, Mootha VK. High-affinity cooperative Ca^{2+} binding by MICU1–MICU2 serves as an on–off switch for the uniporter. *EMBO Rep*. 2017;82:e201643748-201643424.
173. Kohlhaas M, Maack C. Adverse bioenergetic consequences of Na^{+}-Ca^{2+} exchanger-mediated Ca^{2+} influx in cardiac myocytes. *Circulation*. 2010;122:2273-2280.
174. Maack C, Cortassa S, Aon MA, Ganesan AN, Liu T, O'Rourke B. Elevated cytosolic Na^{+} decreases mitochondrial Ca^{2+} uptake during excitation-contraction coupling and impairs energetic adaptation in cardiac myocytes. *Circ Res*. 2006;99:172-182.
175. Luongo TS, Lambert JP, Yuan A, et al. The mitochondrial calcium uniporter matches energetic supply with cardiac workload during stress and modulates permeability transition. *Cell Rep*. 2015;12:23-34.
176. Billia F, Hauck L, Konecny F, Rao V, Shen J, Mak TW. PTEN-inducible kinase 1 (PINK1)/Park6 is indispensable for normal heart function. *Proc Natl Acad Sci U S A*. 2011;108:9572-9577.
177. Hoshino A, Mita Y, Okawa Y, et al. Cytosolic p53 inhibits Parkin-mediated mitophagy and promotes mitochondrial dysfunction in the mouse heart. *Nat Commun*. 2013;4:2308.
178. Kubli DA, Zhang X, Lee Y, et al. Parkin protein deficiency exacerbates cardiac injury and reduces survival following myocardial infarction. *J Biol Chem*. 2013;288:915-926.
179. Nishida K, Kyoi S, Yamaguchi O, Sadoshima J, Otsu K. The role of autophagy in the heart. *Cell Death Differ*. 2009;16:31-38.
180. Youle RJ, van der Bliek AM. Mitochondrial fission, fusion, and stress. *Science*. 2012;337:1062-1065.
181. Shen Z, Li Y, Gasparski AN, Abeliovich H, Greenberg ML. Cardiolipin regulates mitophagy through the protein kinase C pathway. *J Biol Chem*. 2017;292:2916-2923.
182. Ikeda Y, Shirakabe A, Maejima Y, et al. Endogenous Drp1 mediates mitochondrial autophagy and protects the heart against energy stress. *Circ Res*. 2015;116:264-278.
183. Singh SB, Ornatowski W, Vergne I, et al. Human IRGM regulates autophagy and cell-autonomous immunity functions through mitochondria. *Nat Cell Biol*. 2010;12:1154-1165.
184. Huang W, Choi W, Hu W, et al. Crystal structure and biochemical analyses reveal Beclin 1 as a novel membrane binding protein. *Cell Res*. 2012;22:473-489.
185. Kroemer G, Mariño G, Levine B. Autophagy and the integrated stress response. *Mol Cell*. 2010;40:280-293.
186. Sun Y, Yao X, Zhang QJ, et al. Beclin-1-dependent autophagy protects the heart during Sepsis. *Circulation*. 2018;138:2247-2262.
187. Antón Z, Landajuela A, Hervás JH, et al. Human Atg8-cardiolipin interactions in mitophagy: specific properties of LC3B, GABARAPL2 and GABARAP. *Autophagy*. 2016;12:2386-2403.
188. Chu CT, Ji J, Dagda RK, et al. Cardiolipin externalization to the outer mitochondrial membrane acts as an elimination signal for mitophagy in neuronal cells. *Nat Cell Biol*. 2013;15:1197-1205.
189. Petit PX, Ardilla-Osorio H, Penalvia L, Rainey NE. Tafazzin mutation affecting cardiolipin leads to increased mitochondrial superoxide anions and mitophagy inhibition in Barth syndrome. *Cells*. 2020;9(10):2333-2362. https://doi.org/10.3390/cells9102333
190. Hsu P, Liu X, Zhang J, Wang H-G, Ye J-M, Shi Y. Cardiolipin remodeling by TAZ/tafazzin is selectively required for the initiation of mitophagy. *Autophagy*. 2015;11:643-652.
191. Wang S, Li Y, Xu Y, et al. AAV gene therapy prevents and reverses heart failure in a murine knockout model of Barth syndrome. *Circ Res*. 2020;126:1024-1039.
192. Schaloske RH, Dennis EA. The phospholipase A2 superfamily and its group numbering system. *Biochim Biophys Acta*. 2006;1761:1246-1259.
193. Valianpour F. Linoleic acid supplemention of Barth syndrome fibroblasts restores cardiolipin levels: implications for treatment. *J Lipid Res*. 2002;44:560-566.
194. Szeto HH. First-in-class cardiolipin-protective compound as a therapeutic agent to restore mitochondrial bioenergetics. *Br J Pharmacol*. 2014;171:2029-2050.
195. Birk AV, Liu S, Soong Y, et al. The mitochondrial-targeted compound SS-31 re-energizes ischemic mitochondria by interacting with cardiolipin. *J Am Soc Nephrol*. 2013;24:1250-1261.
196. Davey KM, Parboosingh JS, McLeod DR, et al. Mutation of DNAJC19, a human homologue of yeast inner mitochondrial membrane co-chaperones, causes DCMA syndrome, a novel autosomal recessive Barth syndrome-like condition. *J Med Genet*. 2006;43:385-393.
197. Ojala T, Polinati P, Manninen T, et al. New mutation of mitochondrial DNAJC19 causing dilated and noncompaction cardiomyopathy, anemia, ataxia, and male genital anomalies. *Pediatr Res*. 2012;72:432-437.
198. Richter-Dennerlein R, Korwitz A, Haag M, et al. DNAJC19, a mitochondrial cochaperone associated with cardiomyopathy, forms a complex with prohibitins to regulate cardiolipin remodeling. *Cell Metab*. 2014;20:158-171.
199. Cruysberg JR, Sengers RC, Pinckers A, Kubat K, van Haelst UJ. Features of a syndrome with congenital cataract

and hypertrophic cardiomyopathy. *Am J Ophthalmol*. 1986; 102:740-749.

200. Haghighi A, Haack TB, Atiq M, et al. Sengers syndrome: six novel AGK mutations in seven new families and review of the phenotypic and mutational spectrum of 29 patients. *Orphanet J Rare Dis*. 2014;9:119.
201. Sengers RC, Lamers KJ, Bakkeren JA, Schretlen ED, Trijbels JM. Infantile Gaucher's disease: glucocerebrosidase deficiency in peripheral blood leukocytes and cultured fibroblasts. *Neuropadiatrie*. 1975;6:377-382.
202. Calvo SE, Compton AG, Hershman SG, et al. Molecular diagnosis of infantile mitochondrial disease with targeted next-generation sequencing. *Sci Transl Med*. 2012;4:118ra110.
203. Kang Y, Stroud DA, Baker MJ, et al. Sengers syndrome-associated mitochondrial acylglycerol kinase is a subunit of the human TIM22 protein import complex. *Mol Cell*. 2017;67: 457-470.e5.

How to cite this article: Dudek J, Maack C. Mechano-energetic aspects of Barth syndrome. *J Inherit Metab Dis*. 2022;45(1):82-98. doi: 10.1002/jimd.12427