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Review

Cardiolipin in Pathology: Implications in Atherosclerosis

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Abstract: Mitochondria are cell organelles whose main role is to generate the energy needed for cell biochemical reactions via oxidative phosphorylation. Cardiolipin is a phospholipid that is present in the inner mitochondrial membrane and other energy-transducing membranes. Mitochondrial structure largely depends on cardiolipin, as it is involved in the biogenesis of mitochondrial cristae, folds in the inner mitochondrial membrane designed to increase the surface area, as well as in protein-lipid interactions, oxidative phosphorylation, and other essential processes. Cardiolipin is also substantial for mitochondrial supercomplexes' inner mitochondrial membrane and outer mitochondrial membrane architecture. Changes in cardiolipin profile are able to greatly affect mitochondrial function, leading to its impairment and eventually the development of multiple disorders, such as sterile inflammation, atherosclerosis, metabolic disorders, and neurodegenerative disorders. The role of cardiolipin in the proper functioning of mitochondria ought to be investigated in order to find ways to avert the development of many serious disorders. The aim of this review was to examine available data on the causal connection between cardiolipin alterations and the progression of various pathological conditions, as well as possible ways of preventing these adverse conditions. According to existing literature, alterations in cardiolipin are the potential cause of mitochondrial dysfunction, which stimulates the development of various related disorders. Several therapeutic agents (e.g., elamipretide) have shown promising results in preventing adverse effects of cardiolipin alterations.

Keywords: Atherosclerosis, Cardiovascular Disease, Mitochondria, Phospholipids, Cardiolipin

Introduction

A mitochondrion is an organelle that is believed to be a cell's power station. Most of the energy that cells need is generated by mitochondria via Oxidative Phosphorylation (OXPHOS). Mitochondria also participate in reduction-oxidation signaling, programmed cell death, autophagy, calcium homeostasis, and many other mechanisms (Kung *et al*., 2021). There are 2 mitochondrial membranes: Outer and inner mitochondrial membranes. The space between these membranes is called intermembrane space. The mitochondrial cristae are tubular folds of the inner membrane (Klecker and Westermann, 2021). They surround the matrix and nourish the enzymatic complexes that take part in oxidative phosphorylation. Inner and outer membranes mostly consist of Phospholipids (PLs), although the phospholipid compositions are not the same as well as the way they are distributed. They are mostly produced in the Endoplasmic Reticulum (ER) and transported to the mitochondrion. PLs are the key players in the protein translocation into the mitochondria as well as in the membrane structure, activity, and dynamics (Schenkel and Bakovic, 2014). The integrity of the mitochondrial membrane, its permeability, and fluidity may be influenced by changes

in PL composition. This might have an impact on the activity and stability of various proteins related to the Inner Mitochondrial Membrane (IMM), such as the proteins that participate in the electron transport chain and oxidative phosphorylation, with a number of consequences in different health disorders (Ademowo *et al*., 2017). Cardiolipin (CL) is a phospholipid that is localized in the inner mitochondrial membrane and accounts for about 15-20% of all PLs in the mitochondria. Cardiolipin has features that are not typical for PLs, such as dimeric structure, 3 glycerol groups, 4 acyl groups, and 2 phosphatidyl moieties that are connected to the glycerol. This unusual structure makes cardiolipin cone-shaped which is the source of its ability to sense curvature (Paradies *et al*., 2019). Available data indicate that cardiolipin is needed to produce energy, provide cellular respiration, and other mitochondrial metabolism processes. Moreover, CL takes part in the stability and morphology of mitochondrial cristae, biogenesis, mitochondrial quality control, mitochondrial fission and fusion dynamics, import of proteins, mitophagy, and a number of stages of apoptosis (Dudek, 2017). Cardiolipin largely consists of unsaturated fatty acids and is located in the inner mitochondrial membrane close to electron transport chain complexes, where Reactive Oxygen Species (ROS) is mainly produced. Thereby, it can easily be peroxidized, which would have an impact on numerous cardiolipin-dependent processes (Panov and Dikalov, 2020). Furthermore, oxidized cardiolipin stored in the outer mitochondrial membrane acts as a signaling platform in the process of apoptosis, stimulating the release of cytochrome complex into the cytosol and the opening of the Mitochondrial Permeability Transition Pore (MPTP). It is quite possible that the changes in the cardiolipin profile can have adverse effects on the activity of the electron transport chain complex, oxidative phosphorylation complex, and many other mitochondrial proteins and enzymes, hereby impairing its function and dynamics (Paradies *et al*., 2019).

Cardiolipin Overview

Cardiolipin Structure and Biosynthesis

Cardiolipin (1,3-bis(sn-3'-phosphatidyl)-sn-glycerol) is an anionic PL consisting of 2 molecules of phosphatidic acid connected by a glycerol moiety. Cardiolipin was originally found in a cow heart by Mary Pangborn (Wang *et al*., 2007). Cone-shaped cardiolipin has a hydrophobic tail and a polar hydrophilic head. Cardiolipin's unusual structure creates tension in IMM and Outer Mitochondrial Membrane (OMM), it is also considered to be essential for CL function in the membranes. Furthermore, the cardiolipin negative charges contribute to its interplay with the membrane proteins, which can be the reason why cardiolipin is detected in large amounts in cristae membranes (Li *et al*., 2015). Mitochondrial cristae membranes carry a charge. During OXPHOS electrons are passed via the electron transport chain, and protons are pumped out of the matrix of the mitochondrion, which generates an electrochemical gradient across the membrane, creating a negative charge on the inner side of the mitochondrial membrane (Joubert and Puff, 2021).

The molecular species of cardiolipin may vary across tissues. e.g., in mammal hearts, it is mostly (80-90%) composed of linoleic acid (C18: 2), with tetralin oleoyl-CL (L_4CL) as the most common species. Normal functioning of the mitochondria largely depends on the tissue-specific cardiolipin acyl chain composition. e.g., OXPHOS and electron transport chain processes in the heart require L_4CL enrichment. Reduced L_4CL in the cardiolipin heart profile leads to mitochondrial dysfunction (Zhou *et al*., 2016). A number of researches have demonstrated that an impairment in the tissue-specific cardiolipin acyl chain composition may cause a reduction in cardiolipin mass and is critical for the development of heart pathophysiology. Whereas L_4CL is of great importance for the normal functioning of mitochondria, the introduction of other fatty acids instead of linoleic acid results in attenuated protein activity in the inner mitochondrial membrane. e.g., elevated concentrations of Docosahexaenoic Acid (DHA) (22: 6) in cardiolipin acyl chain composition augment the mitochondrial membrane fluidity and thus disrupt lipid-protein interactions (Snoke *et al*., 2022).

In mammals de novo synthesis of cardiolipin starts with catalysis of Cytidine Triphosphate (CTP) and Phosphatidic Acid (PA) by Tam41 protein (also referred to as CDP-DAG synthetase), which leads to their transformation into CDP-DAG (Blunsom and Cockcroft, 2020). Then begins the synthesis of Phosphatidylglycerophosphate (PGP) via phosphatidyl group transport from Cytidine Diphosphate Diacylglycerol (CDP-DAG) to sn-1 position of glycerol-3-phosphate that is catalyzed by phosphatidylglycerol phosphate synthase. After that Phosphatidylglycerophosphatase and Protein-Tyrosine Phosphatase 1 (PTPMT1) triggers PGP dephosphorylation which results in the formation of Phosphatidylglycerol (PG). The process of nascent cardiolipin synthesis ends with the condensation of PG with a CDP-DG molecule catalyzed by cardiolipin synthase (Acoba *et al*., 2020).

After nascent cardiolipin is synthesized, it is then deacylated and resynthesized. PLA2 can deacylate nascent cardiolipin to monolysocardiolipin. Then mature cardiolipin undergoes remodeling by the tafazzin gene (Taz), MLCLAT-1/HADHA or ALCAT1. Cardiolipin is

resynthesized in mitochondria by the tafazzin gene and MLCLAT-1/HADHA (Hsu *et al*., 2015). Small parts of monolysocardiolipin are resynthesized by ALCAT1 to mature cardiolipin in Mitochondria-Associated Membrane (MAM). Mature cardiolipin is formed as a result of acyl chain transfer from fatty Acyl-CoA to monolysocardiolipin by acyltransferases ALCAT1 and MLCLAT-1/HADHA. In Barth syndrome lymphoblasts, an MLCLAT-1 compensatory activation was detected (Duncan, 2020). Transfection of Barth syndrome lymphoblasts with MLCLAT-1 construct led to an increase in cardiolipin levels and stimulated mitochondrial function by decreasing mROS, thus ameliorating proton leak and basal respiration. In contrast to MLCLAT-1, ALCAT1 is associated with pathogenic cardiolipin remodeling causing an exacerbation of mitochondrial dysfunction and Oxidative Stress (OS) (Song *et al*., 2019).

Cardiolipin Function

Cardiolipin plays a major role in mitochondrial functioning and structure, bioenergetic function, cristae genesis and organization, IMM and OMM architecture, OXPHOS, protein-lipid interaction, and assembly of mitochondrial supercomplexes (Paradies *et al*., 2019). A considerable amount of cardiolipin is accumulated in mitochondrial cristae, which are meant to increase the surface area of the IMM and thus facilitate OXPHOS, respiration, and other bioenergetic processes. Moreover, cardiolipin is crucial for mitochondrial fission and fusion dynamics as well as apoptotic processes (Gasanoff *et al*., 2021). Cardiolipin is necessary for normal functioning of respiratory supercomplexes consisting of nicotinamide adenine dinucleotide hydrogen-ubiquinone oxidoreductase (complex I), coenzyme Q: Ubiquinone-cytochrome c oxidoreductase (complex III), enzyme cytochrome c oxidase (complex IV) and adenosine triphosphate synthase (complex V). Disruption in cardiolipin synthesis, metabolism, or remodeling can cause metabolic disorders, such as cardiovascular disease, Type 2 Diabetes Mellitus, and the rare condition Barth syndrome. Cardiolipin deficiency caused by taffazin mutations has an impact on mitochondrial biogenesis and can noticeably inhibit the synthesis of adenosine triphosphate. Furthermore, it can impair mitochondrial morphology and organization of the inner mitochondrial membrane (Shinzawa-Itoh *et al*., 2016).

Cardiolipin contains 2 negatively charged phosphates and hereby induces negative curvature of the membrane. As a result, cardiolipin can capture protons at the inner mitochondrial membrane as well as interact with proteins in the inner and outer mitochondrial membranes. Cardiolipin is essential for the activity of adenosine diphosphate/adenosine triphosphate carrier and six cardiolipin molecules strongly bond to it (Dudek, 2017). Cardiolipin synthase deficiency leads to a decrease in cardiolipin levels and causes mitochondrial dysfunction by impairing mitochondrial membrane potential and thus attenuating the activity of adenosine diphosphate /adenosine triphosphate carrier on the inner mitochondrial membrane. Reduced levels of cardiolipin impair the inner mitochondrial membrane proton gradient, which has an impact on the microenvironment of the inner mitochondrial membrane and can inhibit the activity of respiratory enzymes and protein carriers, causing impairment of the membrane proton gradient (Huang *et al*., 2008). The cone-shaped cardiolipin with a negative charge facilitates its interaction with various proteins including PHBs, SLP-2, MICOS, and MAP1LC3. PHBs are proteins that are located in the inner mitochondrial membrane, they participate in PL homeostasis and cell signaling. KD of PHB2 was reported to be able to change cardiolipin molecular composition in HEK293 cells. MICOS is a large protein complex that is found in crista junctions. It is essential for the formation of cristae structure and is involved in interaction with cardiolipin and cell membranes (Li *et al*., 2020). MAP1LC3 serves as an autophagosome recruitment marker. Apoptotic processes involve cardiolipin as a major player. In apoptosis mediated by mitochondria, cardiolipin recruits caspase-8 to the outer mitochondrial membrane (Bloemberg and Quadrilatero, 2019). Cardiolipin is necessary to recruit tBid and other pro-apoptotic proteins from cytosol to the inner mitochondrial membrane. Furthermore, cardiolipin is substantial for mitophagy, a means of removing damaged mitochondria through autophagy via interplay with various proteins (Manganelli *et al*., 2021).

The stability of mitochondrial supercomplexes, their architecture, and proper functioning depend on cardiolipin. Lack of cardiolipin may cause disruption of supercomplexes and inhibit the production of energy. Thereby, cardiolipin serves as a linchpin that supports and holds mitochondrial supercomplexes together (Mileykovskaya and Dowhan, 2014). Mitochondrial supercomplexes can be dissociated in the presence of Barth syndrome. In the taffazin KD murine model of Barth syndrome, activity, and generation of supercomplexes were decreased in many tissues. In the presence of supercomplexes disruption, production of mROS elevates, which can cause peroxidation of cardiolipin. The structure of cardiolipin is easily affected by Lipid Peroxidation (LP). Cardiolipin peroxidation triggers apoptotic processes by releasing Cytochrome C (Ghosh *et al*., 2019). Moreover, cardiolipin is located in the inner mitochondrial membrane where mROS is produced, which makes it more sensitive to peroxidation. A discrepancy between mROS and various antioxidant enzymes, e.g., superoxide dismutase, can induce cell and mitochondrial injury considerably (Miranda-Díaz *et al*., 2019).

Mitochondria-Driven Sterile Inflammation in Atherosclerosis

A major part of Atherosclerosis (AS) pathogenesis is sterile inflammation. A disruption of phagocytosis of oxidized Low-Density-Lipoprotein (LDL) by macrophages can cause inflammation and stimulate AS development. Sterile inflammation is different from the classic one, as the former is induced by foreign invaders, and the latter is induced by endogenic components released from injured cells (Kourtzelis *et al*., 2021). These endogenic mediators are referred to as Damage-Associated Molecular Patterns (DAMPs). They are formed from the cell nucleus, cell membrane, proteins in cells, and mitochondria. DAMPs are distinguished by specific receptors which then stimulate an immune reaction. Damage-associated molecular patterns are believed to induce inflammation when released from the cell into extracellular space (Roh and Sohn., 2018), some mitochondrial Damage-Associated Molecular Patterns (mDAMPs), mDNA among them, induce immune reactions when released into the cytoplasm, thus promoting the development of AS and other disorders (Grazioli and Pugin, 2018).

Remarkably, the description of mitochondrial evolution by the endosymbiotic theory allows us to conclude that it supports the idea that mitochondrial contents act as damage-associated molecular patterns that promote sterile inflammation. Usually foreign and conserved bacteria are recognized by the Innate Immune System (IIS) which protects the organism against infection (Rossmann *et al*., 2021). Although, it is not the same with mitochondrial damage-associated molecular patterns. Since a mitochondrion is a result of the endosymbiotic evolution of alphaproteobacteria, its contents have many similar features. Toll-like receptor 9 is an important receptor in the inflammation mechanism induced by mDNA. It is mainly localized in the DNA of bacteria and viruses. Toll-like receptor 9 finds unmethylated 5'-C-Phosphate-G-3' (CpG) sequences in the DNA (Andrieux *et al*., 2021). However, there are unmethylated repeats of CpG DNA in the mitochondrial DNA, which promotes inflammation the same way that the DNA of bacteria and viruses promotes it when released from injured cells. Correspondingly, N-fMet-tRNA is essential for both mitochondrial translation and bacterial DNA translation. When it is released from damaged cells, it stimulates the same inflammatory reactions as bacteria. It is noteworthy that mDAMPs functioning and ability to promote the (IIS) Insulin/Insulin-Like Growthfactor-1 Signaling reaction is mainly a result of their evolutional connection to alphaproteobacterial (Wang *et al*., 2021).

In addition, a set of mitochondrial contents was found to function as damage-associated molecular patterns to promote and support reactions of the immune system in various disorders. If the mitochondrial function is impaired, the released mDAMPs trigger AS by maintaining sterile inflammation and enhancing plaque sensitivity. e.g., cell-free circulating mitochondrial DNA serves as a damage-associated molecular pattern by enhancing toll-like receptor 9 to activate nuclear factor-κB signaling, which results in the expression of pro-inflammatory cytokine (Nakahira *et al*., 2015). Moreover, it has been found that ROS, cytosol mDNA, HSP 60, TFAM, FMIT, Cyt C, and cholesterol crystals act as mitochondrial DAMPs. Cardiolipin is usually localized in the IMM and functions as a damage-associated molecular pattern via its sensitivity to inactivation by oxidation or its translocation to the OMM, which triggers a signaling response stimulating mitophagy. Furthermore, the reduced balance between Nicotinamide Adenine Dinucleotide (NAD) and NAD serves as an indicator for mitochondrial DAMPs (Koenig and Buskiewicz-Koenig, 2022). On the whole, mitochondrial DAMPs pass through inflammasome-dependent mechanisms and stimulate plaque formation and AS by maintaining the signaling of sterile inflammation. Additionally, mitochondrial DAMPs activate the NLR family pyrin domain containing 3 inflammasomes. It is a multi-protein complex that includes the NLR family pyrin domain containing 3, PYCARD, and interleukin-1 converting enzyme (caspase-1), which results in proteolytic activation of pro-IL-1 beta to IL-1 beta. Finally, oxidative stress and reactive oxygen species recruit monocytes and activate pro-inflammatory reactions, thus contributing to the progression of AS (Liu *et al*., 2014).

Cardiolipin in Inflammation

Since CL is a mitochondrial DAMP, it takes part in stimulating sterile inflammation and the development of AS. If mitochondria don't function properly, CL is moved from the IMM to the OMM through PLSCR3 and then released to the extracellular environment. However, CL is very sensitive to oxidation because of its unsaturated FA components (Cruz and Kang, 2018). Hereby, oxidized CL is found in the apoptotic cells of AS plaques, which supports the idea that it promotes sterile inflammation causing the development of AS. In the apoE-deficiency murine model and in the human model of CAD, various autoantibodies were reported to bind to oxidized CL which correlated with the development of AS and acted as indicators of LP. Recent research demonstrated that subclinical AS is more prevalent in individuals with aPL antibodies such as antiCL (ACA), particularly in the presence of elevated CV risk (El-Bahrawy *et al*., 2016).

Oxidized cardiolipin promotes multiple pro-inflammatory mechanisms as they are present in IMM,

OMM, and bacterial membranes. For example, in a healthy murine model, when CL is Bound to a cluster of differentiation 1 d (CD1d), it is then presented to CL-sensitive gamma delta T cells in the liver and spleen, promoting a host response (Maguire *et al*., 2017). Oxidized cardiolipin, when released, undergoes hydrolysis by Lp-PLA2, interacting with inflammation signaling pathways. Moreover, oxidized cardiolipin contributes to the synthesis of LTB_4 by elevating levels of calcium within neutrophils and macrophages and upregulating the expression of 5-LOX. These processes are essential for AS since mRNA levels for 3 main proteins necessary for the synthesis of LTB_4 are found more and more frequently in AS lesions negatively correlating with their stability (Buland *et al*., 2016). Moreover, ICAM-1 and VCAM-1 expression is upregulated in ECs in the presence of oxidized cardiolipin, triggering the recruitment of monocytes to the tunica intima. In addition, CL formed in the membranes of bacteria and mitochondria allures macrophages and promotes phagocytosis by enhancing SR-B3. It is noteworthy that the NLR family pyrin domain containing 3 inflammasomes undergoes recruitment and activation by CL, which binds directly leading to transcription of interleukin-1 beta that exhibits atherogenic function (Lin *et al*., 2019).

Cardiolipin Targeting Therapeutic Agents in Disease

In many diseases secondary complications are a result of mitochondrial function impairment. Changes in cardiolipin components, fatty acyl chain structure, or oxidation level can disrupt mitochondrial function significantly, since cardiolipin is essential for numerous biochemical mechanisms of metabolism of the mitochondria (Nicolson, 2014). Changes in cardiolipin lie at the root of mitochondrial dysfunction related to metabolic syndrome, Barth syndrome, myocardial ischemia, myocardial reperfusion, neurodegenerative disorders, and other pathological conditions. Hereby, agents that are capable of preserving mitochondrial cardiolipin contents can help alleviate mitochondrial damage related to these disorders. A number of compounds targeting cardiolipin were found to be able to prevent mitochondrial dysfunction, hence useful for the treatment of these disorders. Clinical studies of these agents are presently underway (Shi, 2010).

IMM and OMM can be directly targeted by a tetrapeptide elamipretide (also known as SS-31, MPT-131, Bendavia). Elamipretide can reach the inner mitochondrial membrane and bind to cardiolipin via hydrophobic and electrostatic interactions, preventing complex of cytochrome c and cardiolipin from being formed, inhibiting its corresponding peroxidase activity and hereby decreases peroxidation of cardiolipin mediated by reactive oxygen species and ameliorates ability of cytochrome c to carry electrons (Tse *et al*., 2020). Elamipretide and cardiolipin interplay keeps mitochondrial cristae intact and protects its morphology as well as keeps the electron transport chain supercomplexes stable. Elamipretide hereby improves mitochondrial respiration and the production of energy by oxidative phosphorylation, at the same time reducing the production of reactive oxygen species. Elamipretide also takes part in the modulation of mitochondrial quality control processes and mitophagy (Allen *et al*., 2020). This tetrapeptide was reported to be able to selectively promote the absorption of mitochondria by autophagosomes and to repair the damage caused by nutrient surplus in Ins1-beta cells. A number of researches showed that this tetrapeptide successively ameliorates the function of mitochondria, cells, and organs in different disease models which are associated with changes in cardiolipin and mitochondrial function impairment (Chatfield *et al*., 2019). In some animal models, this peptide proved to exhibit a protective function against infarction/reperfusion damage. Administration of elamipretide at the start of reperfusion resulted in a decrease in MI and prevention of left ventricular remodeling. Moreover, it ameliorates cardiac muscle function after the MI, alleviates cardiac fibrosis in the border zone, and recovers the expression of mitochondrial energy metabolism genes (Ye *et al*., 2015). Alterations of cardiolipin contents are associated with mitochondrial function impairment and subsequent disruption of energy production, which makes the mitochondrial function a promising therapeutic target. Recent ex vivo studies explored the elamipretide influence on mitochondrial function in cardiac failure. Human hearts were explanted and studied, the results demonstrated that elamipretide ameliorated mitochondrial respiration and function after heart failure considerably, and upregulated activity of C-I, C-IV, and supercomplex-related complex IV activity (Werbner *et al*., 2023). Moreover, after five days of therapy, this peptide improved physical performance in individuals with Primary Mitochondrial Myopathy (PMM). These discoveries are yet to be verified in larger studies with prolonged therapy in order to find more therapeutic advantages (Karaa *et al*., 2018).

Melatonin is a hormone produced by epiphysis cerebri. It plays an important role in the control of the sleep-wake cycle and protects against oxidative stress. This compound can act as a scavenger of free radicals due to its aromatic indole ring with rich electron content, thus being able to donate electrons. The main free radical source is mitochondria, where melatonin is produced and stored (Ferlazzo *et al*., 2020). Melatonin exhibits its antioxidant function in mitochondria and hereby ameliorates mitochondrial ability to produce energy.

Moreover, melatonin was confirmed to modulate mitochondrial biogenesis, mitophagy, and dynamics, thus supporting proper mitochondrial functioning. Cardiolipin oxidation caused by reactive oxygen species has an impact on a number of mitochondrial bioenergetic characteristics, such as mitochondrial permeability transition pore opening and release of cytochrome complex, which are major apoptotic events. Several *in vitro* trials investigated mitochondria obtained from rat hearts and demonstrated that mitochondrial permeability transition pore opening and release of cytochrome complex are suppressed by melatonin (Reiter *et al*., 2017). This impact can be ascribed to melatonin's capacity to avert oxidation of cardiolipin and peroxidation of the major components of cardiac cardiolipin-linoleic fatty acyl chains. These discoveries are confirmed by the fact that melatonin exhibits the ability to scavenge lipid peroxy radicals ($LOO^{\bullet}$) *in vitro* (Paradies *et al*., 2010). Accordingly, therapy with melatonin demonstrated protective action against mitochondrial dysfunction in rats with myocardial infarction or reperfusion. Melatonin reduces the production of reactive oxygen species, thus averting changes in cardiolipin and the function of respiratory complexes of the electron transport chain as well as suppressing the release of cytochrome complex and mitochondrial permeability transition pore opening (Tan *et al*., 2016). As a result of melatonin therapy in rats, post-infarction hemodynamics were ameliorated and the area of ischemic necrosis was decreased. These research findings were translated into clinical practice. It has been reported that melatonin, when administered to individuals with ST-Elevation Myocardial Infarction (STEMI), substantially decreased the infarct size after Primary Percutaneous Coronary Intervention. Hereby, melatonin therapy can turn out to be a reasonable therapeutic strategy to fight pathological conditions associated with mitochondrial dysfunction, CL alterations, and oxidative stress, e.g., myocardial infarction, Alzheimer's disease, neurodegenerative disorders, Parkinson's disease (Bermudez-Gonzalez *et al*., 2022).

Cationic plastoquinone derivatives (SkQs) are amphipathic antioxidants that are able to enter the mitochondrial membrane PL bilayer and be selectively stored there. These agents exhibit their strong antioxidant function in mitochondria, thus averting or reducing damage caused by oxidative stress (Apostolova and Victor, 2015). SkQs are capable of maintaining cardiolipin integrity by averting its oxidation by reactive oxygen species attack, which is considered one of their protective mechanisms against oxidative damage. Oxidation of cardiolipin is associated with apoptotic processes and mitochondrial dysfunction. Hereby, SkQs can defend mitochondrial function and suppress apoptosis by suppressing the oxidation of cardiolipin. This activity of SkQs can be the reason why they positively affect multiple pathological conditions (Paradies *et al*., 2014a-b).

Conclusion

According to a variety of studies, cardiolipin is critical for a number of mitochondrial biochemical processes. Considerable amounts of cardiolipin are contained in mitochondrial membranes and play an important role in maintaining mitochondrial function. Cardiolipin has been reported to act as Damage-Associated Molecular Pattern (DAMP). DAMPs are endogenic mediators that promote sterile inflammation when released from damaged cells into the extracellular environment. In contradistinction to classical inflammation, sterile inflammation is triggered by endogenic contents alone and not by foreign particles. Sterile inflammation greatly contributes to atherogenesis as a consequence of disrupted phagocytosis of oxidized LDL which induces inflammation and atherosclerosis development. Hereby, alterations in cardiolipin can lead to mitochondrial dysfunction, which results in the development of various related disorders. Several therapeutic agents have shown promising results in preventing adverse effects of cardiolipin alterations. Elamipretide treatment was reported to improve the function of mitochondria, cells, and organs; melatonin therapy was shown to reduce oxidative stress and improve mitochondrial function. These discoveries require further study to fully explore the benefits of this therapeutic approach.

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Author’s Contributions

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Ethics

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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