JACC: ASIA VOL. 3, NO. 4, 2023

STATE-OF-THE-ART REVIEW

A Comprehensive Insight and Mechanistic Understanding of the Lipidomic Alterations Associated With DCM

Shubham Saha, MSc,[a,b] Praveen Singh, MSc,[c,*] Abhi Dutta, MSc,[a,b,*] Hiteshi Vaidya, MSc,[d] Prakash Chand Negi, MD, DM,[d] Shantanu Sengupta, PhD,[c] Sandeep Seth, MD, DM,[e] Trayambak Basak, PhD[a,b]

ABSTRACT

Dilated cardiomyopathy (DCM) is one of the major causes of heart failure characterized by the enlargement of the left ventricular cavity and contractile dysfunction of the myocardium. Lipids are the major sources of energy for the myocardium. Impairment of lipid homeostasis has a potential role in the pathogenesis of DCM. In this review, we have summarized the role of different lipids in the progression of DCM that can be considered as potential biomarkers. Further, we have also explained the mechanistic pathways followed by the lipid molecules in disease progression along with the cardioprotective role of certain lipids. As the global epidemiological status of DCM is alarming, it is high time to define some disease-specific biomarkers with greater prognostic value. We are proposing an adaptation of a system lipidomics-based approach to profile DCM patients in order to achieve a better diagnosis and prognosis of the disease.
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Cardiomyopathies are a diverse group of diseases associated with the myocardium that result from mechano-electrical dysfunction leading to ventricular hypertrophy or dilatation.[1] Dilated cardiomyopathy (DCM) is one of the most common types of cardiomyopathies that can be characterized by left or biventricular dilatation and systolic dysfunction that arise due to thinning and stretching of the ventricular walls.[2] The decline in left ventricular (LV) contractile function, ventricular arrhythmia, and abnormalities in the conduction system lead to progressive heart failure and death.[3] DCM can be classified as either familial (genetic) or idiopathic.[4] Genetic factors include the mutations in the genes encoding for cytoskeletal, sarcomere, or nuclear envelope proteins.[5] Around 30% to 50% of total DCM cases are estimated to be caused by genetic factors.[6] The progression of myocardial dysfunction in DCM is also attributable to different nongenetic factors including inflammation (viral myocarditis or autoimmune disease), nutritive toxic influences (alcohol, drugs, chemo toxins), and metabolic disorders. However, around 60% of DCM cases remain inexplainable etiologically and are commonly known as idiopathic DCM (IDC).[7] Pathophysiological changes perceived in DCM are reduction in stroke volume (ie, the volume of blood pumped out of the left ventricle of the heart during each systolic cardiac contraction) and cardiac output (ie, the volume of blood being pumped by both ventricles of the heart per unit

From the [a]School of Biosciences and Bioengineering. IIT-Mandi, Mandi, India; [b]BioX Center, Indian Institute of Technology-Mandi, Mandi, India; [c]CSIR-Institute of Genomics and Integrative Biology, New Delhi, India; [d]Department of Cardiology, Indira Gandhi Medical College & Hospital, Shimla, India; and the [e]Department of Cardiology, All India Institute of Medical Sciences, New Delhi, India. *Mr Singh and Mr Dutta contributed equally to this work.
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received February 23, 2023; revised manuscript received May 17, 2023, accepted June 3, 2023.

ISSN 2772-3747 https://doi.org/10.1016/j.jacasi.2023.06.001

ABBREVIATIONS AND ACRONYMS

CL = cardiolipin

CMR = cardiac magnetic resonance imaging

DCM = dilated cardiomyopathy

DIA = data-independent acquisition

ETC = electron transport chain

HDL = high-density lipoprotein

ICM = ischemic cardiomyopathy

IDC = idiopathic dilated cardiomyopathy

LC-MS = liquid chromatography-mass spectrometry

LDL = low-density lipoprotein

LV = left ventricular

LVEDD = left ventricular end-diastolic dimension

LVEF = left ventricular ejection fraction

LVRR = left ventricular reverse remodeling

MS = mass spectrometry

MS/MS = tandem mass spectrometry

PUFA = polyunsaturated fatty acid

ROS = reactive oxygen species

time), impairment of ventricular filling and escalation in end-diastolic pressure (ie, the volume of blood in the left ventricle at the end of ventricular filling).[8] DCM also leads to the remodeling of the left ventricle into a spherical shape along with its dilatation.[9] Various compensatory changes in the vascular system are also visible during DCM, such as elevation in wall stress due to an increase in cardiac preload (amount of sarcomere stretch experienced by cardiac muscle cells that is, cardiomyocytes at the end of the ventricular filling during diastole) and afterload (ie, the pressure that must be worked against by the heart to eject blood during systole).[10] It is accompanied by other changes such as an increase in systemic resistance, venous pressure, circulating blood volume, and a decrease in arterial compliance.[11] Moreover, certain neurohormonal changes, which include an increase in catecholamines, vasopressin levels, and natriuretic peptide, a decrease in vagal activity to the heart, and activation of the renninangiotensinogen-aldosterone system, lead to an increase in cardiotoxicity, myocardial oxygen demand, and ventricular wall stress.[12]

Due to geographic variations, patient selection, and changes in diagnostic criteria, determining the incidence and prevalence of DCM are quite challenging. Few epidemiological studies in recent times estimated the global burden of the disease, and the preliminary assessment shows the prevalence of DCM to be 36.5 in 100,000 individuals as per the study performed on the Olmsted county population in Minnesota in the United States.[13] The global picture of DCM prevalence is estimated to be around 1 of 250 to 400 individuals with an incidence rate of 5- to 7 cases per 100,000 individuals per year.[14] Tropical nations have reported a lower prevalence of DCM than developed nations. For instance, Africa, Latin America, and Japan (17/100,000) showed lower populations inflicted with the same.[15] Comparatively, males show significantly higher incidences of DCM compared with females, with the number of male patients almost 3 times more than female patients.[16] The global burden of disease data have shown a massive increase in the incidence of DCM in India in the past 3 decades; a consistent increase in cases over the decades has been reported with 106,460 cases in 1990, 150,507 new cases in 2005, and 207,168 new cases in the year 2019 in India.[17] The dramatic increase in DCM incidence in India is alarming, and it points out the need for better early diagnosis, effective treatments, and efficient preventive strategies against this disease.[18]

Looking at the severity and death rate of DCM disease, early prevention and effective treatment become significantly important. There are diagnostic techniques, such as echocardiographic analysis and/or cardiac magnetic resonance imaging (CMR)-based imaging, that are considered gold standard methods in the detection of phenotypic alterations in DCM. But these techniques are not cost efficient and may have some limitations in terms of defining disease-specific etiology as they cannot differentiate phenotypic overlapping conditions.[19] Additionally, these are not easily available in most developing countries such as India. Thus, elucidation of circulating biomarkers is essential for effective and affordable diagnosis and prognosis of disease-specific phenotypic alterations. The heart utilizes a huge amount of lipids as a source of energy, as 70% of substrates are fatty acid derivatives that provide the raw materials for adenosine triphosphate (ATP) generation.[20] There is evidence that deterioration in heart function is a consequence of an imbalance in the homeostasis between lipid uptake and subsequent oxidation in cardiomyocytes, which ultimately leads to structural myocardial impairment including cardiac fibrosis, myocyte apoptosis, and abnormalities in contractile function.[21] Alteration of different metabolic pathways has been found to contribute to lipid accumulation in the cardiovascular environment, which is associated with lipotoxicity and subsequent myocardial dysfunction.[22] Hence, the identification of such lipids involved in the pathophysiology of myocardial remodeling during DCM will be a landmark in understanding the disease pathogenesis.

LIPIDOMICS: A NEW ARENA TO EXPLORE DCM

Lipids are essential counterparts of the cellular environment that take part in crucial cellular activities such as membrane formation and signaling pathways, and function as a store of energy.[23] The complete lipid profile present in a cell, organelle, tissue, or body fluid is termed a *lipidome*, whereas the complete characterization of such lipids and their biological roles is defined as *lipidomics*.[24] In recent years, the emerging field of lipidomics has proven to be significantly helpful in omics-based disease research. Lipids are complex molecules that pose a challenge for their identification due to their high degree of isomerism. Mass spectrometry (MS) has become the preferred method for lipid analysis due to

its high sensitivity and the ability to characterize the structural details of molecules. The development of advanced MS instruments, tandem MS (MS/MS) methods for lipid analysis, and the coupling of MS with high-performance separation methods have led to rapid growth in lipidomics. In general, lipids are first extracted from the tissue or body fluid (such as plasma) followed by online chromatographical separation with the m/z detection with MS. The separated lipids undergo ionization inside the ion source of the mass spectrometer and are then detected by the mass analyzer.[25]

MS can be coupled with various chromatographic separation techniques such as gas chromatography, ultrahigh-performance liquid chromatography, or supercritical fluid chromatography to separate lipid species based on their chemical composition and enhance lipid identification coverage. Gas chromatography provides comprehensive profiling of total fatty acids from a given lipidome[26]; however, details about complex structure are lost. Normal-phase liquid chromatography, hydrophilic interaction chromatography, and supercritical fluid chromatography yield lipid class separation.[27] Reversed-phase liquid chromatography provides lipid species separation with some overlap between lipid classes.[28] Ion mobility mass spectrometry coupled with other orthogonal analytical techniques can be used to differentiate isomers and delineate molecules into respective classes based on differences in head group, acyl chain length, and degree of unsaturation.[29]

Both targeted and untargeted assays are used for lipidomics analysis. Targeted assays are acquired with triple quadrupole instruments and are robust with a wide dynamic range and high sensitivity. However, the targets need to be programmed in advance, and molecular parameters that are not on the target list during acquisition are missed. Untargeted assays are more popular in lipidomics research and are acquired with instruments such as Orbitrap (Thermo Scientific) or quadrupole time-of-flight instruments, which have high mass resolution (Orbitrap) and faster acquisition speed (quadrupole time-of-flight). Data-dependent acquisition is commonly used for lipidome analysis, which utilizes a full MS1 scan over a predefined mass range and uses this information to select a few ions (top N) for fragmentation and obtain high-quality MS2 spectra linked to their precursors. However, the precursor selection is stochastic, lacks reproducibility, and is not suitable for quantification or characterization of low-abundance molecules. The shortcoming of the data-dependent acquisition technique is somewhat resolved with the application of data-independent acquisition (DIA) techniques such as SWATH, which can acquire comprehensive MS and MS/MS data over an entire range of m/z values and provide characterization and quantitation of even low-abundance lipid species.[30] Since the application of DIA to lipidomics workflow is recent, therefore tools for analyzing DIA-acquired lipidomics data are limited, with more tools in development.

Nuclear magnetic resonance spectroscopy has also been used to study the physical, chemical, and biological properties of lipids. It provides an external magnetic field and records the electromagnetic radiations released by the atomic nuclei.[31] Of all these techniques, the liquid chromatography-mass spectrometry (LC-MS)-based methods are the most popular as they are highly sensitive. They can detect thousands of lipid species with accuracy and precision even with a very low sample amount.[32] However, with limitations such as difficulty in the characterization of isomers and ion suppression of low-abundant species in the presence of some high-abundant lipids, measurement accuracy and detection capability may be affected.[33] Owing to their structural complexity, characterization of lipids such as glycerophospholipids (GPs) have 6 levels of structural information, including lipid class head group, fatty acyl identities, sn-position of acyl groups, location of carbon-carbon double bonds (C=C), the stereochemistry of C=Cs, and the chiral centers in fatty acyl group or identity and location of functional group substitution. Routine lipidomics workflows explore complexity till the first 2 levels, and variation in deeper structural levels leads to a large number of isomeric structures. Since the CID fragment cell installed in most mass spectrometers is unable to cleave nonpolar bonds (C-C or C=C), additional approaches are required to elucidate structural complexity. Approaches such as ozone-induced dissociation,[34] ultraviolet photodissociation,[35] electron impact excitation of ions from organics,[36] metastable atom-activated dissociation,[37] ion/ion reactions via the charge-remote fragmentation mechanism,[38] and radical-directed dissociation[39] are required to elucidate structural complexity. Alternatively, chemical derivatization of C=C to functional groups by coupling photochemical (Paternò-Büchi),[40] epoxidation,[41] and singlet oxygen ($^1\Delta O_2$)-ene reaction[42] with MS/MS generates informative fragments of C=C locations. Although these recent developments are promising, they are in their early stages of development. Despite such limitations, the emerging discipline of MS-based clinical lipidomics is proving to be a valuable tool in understanding disease pathogenesis and identifying biomarkers for early

disease diagnoses and prognosis.[43] Much before the onset of symptoms, many diseases lead to alterations in lipid profiles of body fluids or tissues, hence discovering and studying such critical lipid biomarkers is helpful in deeply understanding the progression of the disease and its monitoring methods. Hence examining alterations in lipid profiles and discovering specific biomarkers for DCM could give us a broader push for early diagnosis and new target treatment of the disease.

INSIGHTS GAINED FROM LIPIDOMICS STUDIES IN DCM

Previous studies have presented the noteworthy role of lipids in DCM pathophysiology. The study carried out in a Finnish population using ultra-high performance LC-MS/MS-based approach with serum samples of DCM patients carrying a *LMNA* mutation has yielded lower levels of TG(49:1) in DCM patients when compared with DCM patients without a *LMNA* mutation. Moreover, correlation analysis between lipidomic changes and CMR parameters, for example, LV end-diastolic wall thickness and LV wall motion, has established a positive association of altered lipids with cardiac structure and volume changes, and was helpful in assessing the development of disease and its prevention.[44] Ultra-high performance LC-MS and a machine learning-based approach were undertaken to assess candidate lipids in pediatric DCM patients from a Chinese population. The levels of lysophosphatidic acids have been shown to predict LV reverse remodeling (LVRR) in these pediatric DCM cases, and when combined with LV end-diastolic dimension (LVEDD) score, its levels could monitor the effects of anti-heart failure pharmacotherapy.[45] The beneficial role of n-3 polyunsaturated fatty acids (PUFAs) was assessed using *fat-1* transgenic mice in which pressure overload was induced by transverse aortic constriction for 8 weeks. The *fat-1* gene codes for the enzyme n-3 fatty acid desaturase, which converts n-6 PUFAs to n-3 PUFAs. Elevated levels of n-3 PUFAs due to *fat-1* transgenesis unveiled a role in the reduction of cardiac remodeling in terms of improved LV ejection fraction (LVEF) and reduced LVEDD, thereby displaying a protective role against DCM.[46] In another study comprising serum samples of IDC cases and matched healthy control subjects from an Italian population, lower levels of high-density lipoprotein (HDL) cholesterol, apolipoprotein A-I, and apolipoprotein A-II, and higher levels of low-density lipoprotein (LDL) cholesterol and apolipoprotein B were seen to be associated with IDC.[47] A study including children with DCM from a French population comparatively analyzed the acylcarnitine profiles of the participants and showed that highly altered fatty acid oxidation leads to a significantly elevated level of total acylcarnitines and long-chain chain acylcarnitines.[48] In an American population-based study, tissue from the left ventricle of explanted hearts of patients with ICD was analyzed for changes in cardiolipins (CLs) through MS-based methods, and the study exhibited a decrease in tetra-linoleic CLs in the failing hearts.[49] Similarly, when performed on subsarcolemmal and interfibrillar cardiac mitochondria isolated at 5 months and 15 months from rat models of heart failure, a decrease in the level of tetra-linoleoyl CL along with an increase in CL species with oleic and arachidonic acid side chains was also shown.[49] Another LC-MS/MS-based study was performed on 8 DCM patients within an American population in order to examine the role of δ-6-desaturase (D6D) enzyme in the fatty acid redistribution of myocardial phospholipids in a pressure overload condition. This enzyme is the key player in the fatty acid biosynthesis pathway.[50] Elevation in the product-precursor ratio of PUFAs represents the hyperactivity of the D6D enzyme along with the depleted levels of the precursors such as linoleic acid and corresponding elevation in arachidonic and docosahexaenoic acid phospholipid species levels, which was reverted by a LV assist device.[51] This pattern was also replicated in in vivo models when a D6D inhibitor was administered in lean male spontaneously hypertensive heart failure (SHHF) and transverse aortic constriction rats.[51] Moreover, administration of D6D in these experimental rats also normalized the CL composition in the failing heart, which indicates that inhibition of fatty acid metabolism through D6D inhibitor ultimately results in attenuation of cardiac hypertrophy, fibrosis, and contractile dysfunction.[51] In another in vivo mouse model-based study, DCM was induced by modulating the Hippo signaling pathway through transgenesis of the *Mst-1* gene in mice, which is a key kinase downstream of this signaling cascade.[52] This resulted in alterations of the fibrotic and mitochondria-related genes in the transcriptome level, along with the mitochondrial structural abnormalities and perturbation of mitochondrial signature lipids, that is, down-regulation of ubiquinone and CLs, and up-regulation of acylcarnitines. Moreover, mitochondrial metabolic activity was also disrupted as ATP content got depleted along with significant up-regulation in the glycolytic pathway, lactate, and BCAA accumulation in mitochondria.[53] A comparative study between 18 ischemic cardiomyopathy (ICM) and 38 DCM patients showed glycerophospholipid and alpha-linoleic acid metabolism to be significant in

TABLE 1 Summary of Lipidomics Studies Performed in DCM Patients

Focus Population	No. of DCM Patients	Age Group	Study Description	Outcome	First Author, Year
Finnish	8 (11 with risk of DCM)	3-56 y	UPLC-MS/MS for lipid quantification, CMR, and analysis of correlation between lipids and CMR parameters	level of TG(49:1) alteration in LMNA+ individuals, association of lipidomic changes with CMR parameters	Sysi-Aho et al, 2011[44]
Chinese	83	22 mo (DS), 15 mo (VS)	UPLC-MS for lipid metabolites quantitation, OPLS-DA, and RF analysis to screen candidate lipids	4 LysoPAs as independent predictor of LVRR	Wen et al, 2021[45]
Italian	55	55 ± 12 y	Total serum cholesterol, triglycerides, and HDL levels were assessed in IDC patients and matched control patients	Higher TG and lower HDL levels in IDC patients compared with control patients	Sampietro et al, 2005[47]
French	16	3 mo-15 y	Acylcarnitine profiles were checked in children with DCM-HF.	Elevated levels of total acylcarnitine and long chain acylcarnitines were observed.	Lefort et al, 2022[48]
American	10	52 ± 3 y	Cardiolipin was analyzed by MS in human hearts explanted from patients with dilated cardiomyopathy	Decrease in the level of tetralinoleoyl cardiolipin in the failing heart.	Sparagna et al, 2007[49]
American	8	39-65 y	Compositional analysis of phospholipids from hearts explanted from patients with dilated cardiomyopathy	lower levels of linoleic acid with reciprocally higher levels of arachidonic and docosahexaenoic acids were observed	Le et al, 2014[51]
Chinese	38	57.2 ± 10.2 y	Metabolomics analysis by UPLC-MS/MS in DCM, ICM, and healthy control subjects	lysophosphatidylinositol (16:0/0:0), phosphatidylglycerol (6:0/8:0), fatty acid esters of hydroxy fatty acid (24:1), and phosphatidylcholine (18:0/18:3) may have the potential to differentiate patients with DCM and ICM	Zhao et al, 2020[54]
American	54	0-18 y	Analysis of cardiolipin levels in LV tissue samples by LC-MS	Significantly lower total and (18:2)4CL content were demonstrated in myocardium from pediatric patients with IDC compared with NF control patients	Chatfield et al, 2014[55]
American	39	52.1 ± 10.9 y (cohort 1) 50.9 ± 11.6 y (cohort 2)	Plasma and cardiac tissue metabolomics, genome-wide RNA sequencing, and proteomic studies to examine the metabolic status in 87 explanted human hearts from 39 patients with end-stage HF compared with 48 nonfailing donors	Down-regulation of fatty acids and acylcarnitines in affected tissues despite up-regulation in the plasma, along with a marked reduction in ceramides and elevation in lysoglycerophospholipids	Flam et al, 2022[56]

CMR = cardiac magnetic resonance imaging; DCM = dilated cardiomyopathy; DS = discovery set; HDL = high-density lipoprotein; HF = heart failure; IDC = ischemic cardiomyopathy; LC-MS = liquid chromatography-mass spectrometry; LV = left ventricular; LVRR = left ventricular reverse remodeling; LysoPA = lysophosphatidic acid; MS = mass spectrometry; NF = nonfailing; OPLS-DA = orthogonal projections to latent structures discriminant analysis; RF = random forest; TG = triglyceride; UPLC-MS/MS = ultra-high performance liquid chromatography tandem mass spectrometry; VS = validation set.

DCM patients.[54] A major cardiac phospholipid present in the mitochondrial inner membrane, that is, CL, is important for the functioning of energy-producing enzymes in the electron transport chain (ETC). Biosynthesis of the same was seen to be hampered in children with IDC, which leads to myocyte CL depletion and lower levels of (18:2)4 CL.[55] However, an LC-MS-based study on LV tissue samples and plasma samples of DCM patients of different races and sex (4 black men, 5 white men, 4 black women, and 5 white women) showed no significant differences in metabolic contents, which suggests that sex and race do not affect metabolic profiles. However, levels of fatty acids, acylcarnitines, and ceramides were found to be decreased in DCM hearts, but increased levels of the same were observed in the plasma.[56] In fact, increased tissue glucose, pyruvate level, lactate burning, and a decrease in the tricarboxylic acid cycle intermediate metabolite levels are representative of metabolic dysfunction[56] (**Tables 1 to 3**). Accumulation of excess lipids in the myocardium ultimately leads to LV mass increase and impairs cardiac function by causing lipotoxicity to the cardiac muscle cells, leading to cell death.[57] Excessive myocardial fat also possess a high risk of calamitous metabolic consequences in the form of oxidative stress and mitochondrial dysfunction,[57] which is 1 of the main causes of DCM. To examine the contribution of cardiac steatosis (excessive fat accumulation around the myocardium) to the pathophysiological development of DCM, Graner et al[57] performed a CMR-based study in 10 nondiabetic men with DCM and 20 healthy control subjects. Myocardial triglyceride (TG) content was found to be significantly lower in DCM patients, although epicardial and pericardial fat accumulation was remarkably higher in the DCM group compared with the control patients. LV mass, LV end-systolic dimension, and LVEDD are significantly elevated and LVEF is reduced in DCM patients.[57] Further, Nyman et al[58] using CMR and proton magnetic spectroscopy showed that LV diastolic dysfunction was associated with metabolic syndrome and that

TABLE 2 Summary of Lipidomics Studies Performed in Model Systems of DCM

Animal/Cell Line	Age	DCM Induced by:	Study Description	Outcome	First Author, Year
Fat-1 transgenic C57BL/6 mice	8 wk	Transverse aortic constriction	Examination of the effects of n-3 PUFA in the heart by mRNA sequencing, label-free phosphoprotein quantification, lipidomics, WB, RT-qPCR, and ATP detection	Endogenous n-3 PUFAs prevent dilated cardiomyopathy via orchestrating gene expression, protein phosphorylation, and lipid metabolism	Li et al, 2022[46]
Mst1 transgenic mice	3 wk and 6 mo	Overexpression of Mst1	Assessment of mitochondrial abnormalities by electron microscopy, RNA seq, cardiotranscriptome and lipidome analysis, ATP and ROS detection	Hippo signaling activation mediates mitochondrial damage by repressing mitochondrial genes, which causally promotes the development of DCM	Wu et al, 2021[53]
SHHF rat	2 mo		Cardiolipin molecular species and cytochrome oxidase (COX) activity were studied in IF and SSL cardiac mitochondria by mass spectrometry, mitochondrial enzyme activity assay and WB	A progressive loss of cardiac L4CL, possibly attributable to decreased remodeling, occurs in response to chronic cardiac overload, but not ageing alone, in both IF and SSL mitochondria	Sparagna et al, 2007[49]

ATP = adenosine triphosphate; DCM = dilated cardiomyopathy; IF = interfibrillar; PUFA = polyunsaturated fatty acids; ROS = reactive oxygen species; RT-qPCR = real-time quantitative polymerase chain reaction; SSL = subsarcolemmal; WB = Western blotting.

epicardial and pericardial fat deposition were inversely correlated with LV diastolic function in men with metabolic syndrome. However, unlike the previously mentioned instance, all epicardial, myocardial, and pericardial fat accumulation was comparatively higher in patients than in control subjects.[58] Hence, both study outcomes indicate that epicardial and pericardial fat depots are related to structural and functional abnormalities of the heart, though the correlation between myocardial fat accumulation and the cardiac anomaly is subject to future investigations.

MECHANISTIC UNDERSTANDING OF DCM ASSOCIATED WITH THE LIPIDOMICS STUDIES. DCM is a cardiac disease with varied etiologies. There are numerous alterations in cellular signaling that significantly contribute to the disease progression of DCM.

Reactive oxygen species and Mitochondrial dynamics. Mitochondrial dysfunction is one of the leading causes where excessive production of reactive oxygen species (ROS) hampers normal cellular function and forces the cell towards apoptosis.[40] The prime ROS generated in cardiac mitochondria is superoxide radical anion, which is a toxic derivative of the oxidative phosphorylation pathway. ROS generation in the cardiac mitochondrial environment is significantly associated with CL.[59] CL content plays a crucial role in maintaining the structural integrity and optimal enzymatic activity of complexes involved in the ETC.[59] Biochemical analysis of CL clearly indicates the presence of a specific binding site for complex I,[60] III,[61] and IV[62] in CLs, which is essential for supercomplex formation among enzyme complexes of the mitochondrial ETC. This supercomplex improves the efficiency of electron translocation and reduces the risk of ROS formation.[63] Chatfield et al[55] have shown that total CL content along with (18:2)4CL have been significantly decreased in the LV tissue of 54 pediatric IDC patients. A similar level of (18:2)4CL was also evident in the myocardium of 2-month-old SHHF rats.[49] These observations clearly indicate the onset of pathogenic conditions in the cardiac environment with the alteration of specific CL content of the myocardium.

In pathogenic conditions, a large amount of O_2^- is produced as it cannot be reduced completely by electrons due to the leakage of electrons through complex I and complex III.[64,65] Moreover, there are certain mitochondrial enzymes, namely NADPH oxidase 4 (NOX4), that get up-regulated in failing hearts and further contribute to generating oxidative stress in the cardiac environment.[66] As ROS reaches its threshold level, it causes the opening of the mitochondrial permeability transition pore (mPTP). mPTP opening is preceded by the CL peroxidation where ROS is a major contributor.[67] The mPTP consists of a group of inner and outer mitochondrial proteins, namely voltage-dependent anion channel (VDAC), ADP:ATP antiporter (ANT), and peptidyl-prolyl cis-trans isomerase cyclophilin D. Peroxidized CLs interact with ANT to trigger the mPTP opening[68] and facilitate the release of ROS in the cytosol to increase the ROS concentration in cardiomyocyte cytoplasm[69] (**Figure 1**).

The cardiomyocyte cytoplasm contains numerous signaling proteins that critically regulate different cellular activities in order to the proper functioning of the heart. Thioredoxin (Trx) is 1 such protein, which in its reduced form shows its inhibitory effect on

apoptosis signal-regulating kinase 1 (ASK1) by binding it.[70] Accumulation of ROS in cardiomyocyte cytoplasm ultimately results in the oxidation of Trx and subsequent dissociation of Trx from ASK1.[71] ASK1 is a 1,374 amino acid-containing protein with a centrally located serine-threonine kinase domain and a crucial member of the mitogen-activated protein kinase (MAPK) family. It elicits its effect by activating p38 MAPK in response to various stress stimuli.[72] After dissociation from Trx, ASK1 further phosphorylates p38 MAPK which subsequently activates a downstream effector molecule Seven in absentia homolog 2 (Siah2).[73] Siah2 is a member of the E3 ubiquitin ligase family and mediates ubiquitination followed by proteasomal degradation of target protein, chiefly A-kinase anchor protein 121 (AKAP121) in cardiomyocytes. AKAP121 significantly contributes to mitochondrial dynamics through protein kinase A (PKA)-dependent inhibitory phosphorylation of dynamin related protein 1 (Drp1). Siah2-driven proteasomal degradation of AKAP121 ultimately releases Drp1 from inhibitory phosphorylation, resulting in mitochondrial fission[74] (**Figure 1**).

ROS-induced alterations in mitochondrial dynamics are also related to the activation of receptor tyrosine kinases (RTK).[75] The binding of ROS to the RTK results in the conversion of guanosine diphosphate (GDP)-bound RAS to its activated guanosine triphosphate (GTP)-bound state, directed by the guanine nucleotide exchange factor (GEF) to relay the downstream signaling cascade.[76] RAS is also having an oxidative stress sensor domain consisting of a cysteine residue in a conserved consensus signature sequence NKXD, where X represents the red-ox sensing cysteine. This cysteine residue gets oxidized in response to the excess ROS accumulation in the cytosol.[77] Activated RAS further transduces ROS stimulation to downstream effectors consisting of Raf, mitogen-activated protein kinase (MEK), and extracellular signal regulated kinase 2 (ERK2) to promote phosphorylation of Drp1 at Ser616, resulting in mitochondrial fragmentation.[78]

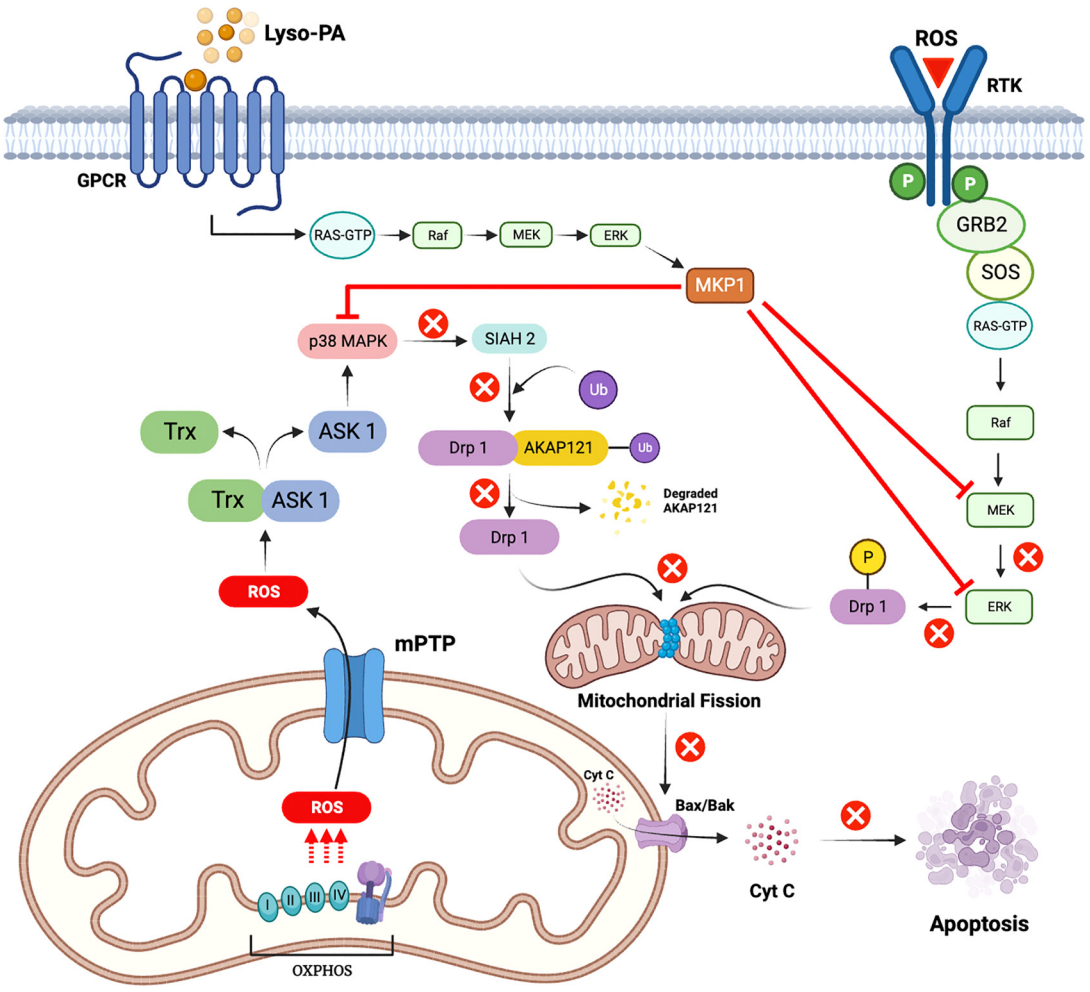
There is a correlation between the mitochondrial fission and apoptotic machinery as Drp1 and different pro-apoptotic factors such as Bcl-2 associated X-protein (Bax) and Bcl-2 homologous antagonist killer (Bak) colocalize at the large foci of mitochondrial fission sites.[79] Bax is normally localized in the cytosol, and Bak is mostly distributed in the outer mitochondrial membrane in a healthy cardiomyocyte. Bax translocates from the cytosol to the mitochondrial outer membrane upon activation of the mitochondrial fission machinery and triggers mitochondrial outer membrane permeabilization. As a result, cytochrome c is released into the cytosol and allosterically activates apoptosis protease activating factor 1 (APAF1), further contributing to the proteolytic maturation of caspase 3 and caspase 9.[80] Activated caspase promotes apoptosis of cardiomyocytes, which is the hallmark of DCM disease progression. Cytochrome c release in the myocardial cytoplasm is a consequence of CL peroxidation and translocation of CLs from the inner mitochondrial membrane to the outer mitochondrial membrane.[59] Cytochrome c mediates electron transfer between complexes III and IV of the ETC and remains bound to CLs. As the ROS targets the unsaturated fatty acyl chains of CLs, cytochrome c loses its interaction with oxidized CLs and gets released during apoptosis.[81] Moreover, the translocation of CLs from the inner mitochondrial membrane to the outer mitochondrial membrane, mediated by mitochondrial phospholipid scramblase-3 (PLS-3), mitochondrial creatine kinase (MtCK), and nucleoside diphosphate kinase (NDPK-D), serves as a prerequisite for providing platforms to different proteins participating in apoptotic signal activation, the most important being the oligomerization, membrane insertion, and pore formation by Bax and Bak proteins[82-84] (**Figure 2**). Modulation in the activity of key kinases involved in this pathway has been estimated to be interfered with by a dual specificity phosphatase, namely mitogen-activated protein kinase phosphatase 1 (MKP1), that ultimately leads to LV reverse remodeling in pediatric DCM cases.[45]

TABLE 3 Summary of Sources of Altered Lipids in DCM Patients

Lipids	Source
TG(49:1)	Exogenous from dietary fat; endogenous from the liver[44]
LysoPAs	Activated platelets, leukocytes, and fibroblasts[45]
HDL	Exogenous from dietary fat; endogenous from the liver[47]
Acylcarnitine	Reduced beta-oxidation of long-chain fatty acids of the myocardium[48]
Tetralinoleoyl cardiolipin	Cardiac mitochondrial inner membrane[49]
Linoleic acid	Diet; myocardial phospholipid pool[51]
Arachidonic acid	Diet; myocardial phospholipid pool[51]
Docosahexaenoic acid	Diet; myocardial phospholipid pool[51]
Lysophosphatidylinositol (16:0/0:0)	Bioactive lipid generated by phospholipase A (PLA)[54]
Phosphatidylglycerol (6:0/8:0)	Mitochondrial inner membrane[54]
Phosphatidylcholine (18:0/18:3)	Circulating lipoproteins[54]
Ceramides	Within cardiomyocytes, ceramides derive from the condensation of palmitate and serine to a sphingoid base or through salvage pathways[56]
Lysoglycerophospholipids	Lysoglycerophospholipids derive from phospholipids. Phospholipids constitute about 7% of myocardial dry weight[56]

Abbreviations as in **Table 1**.

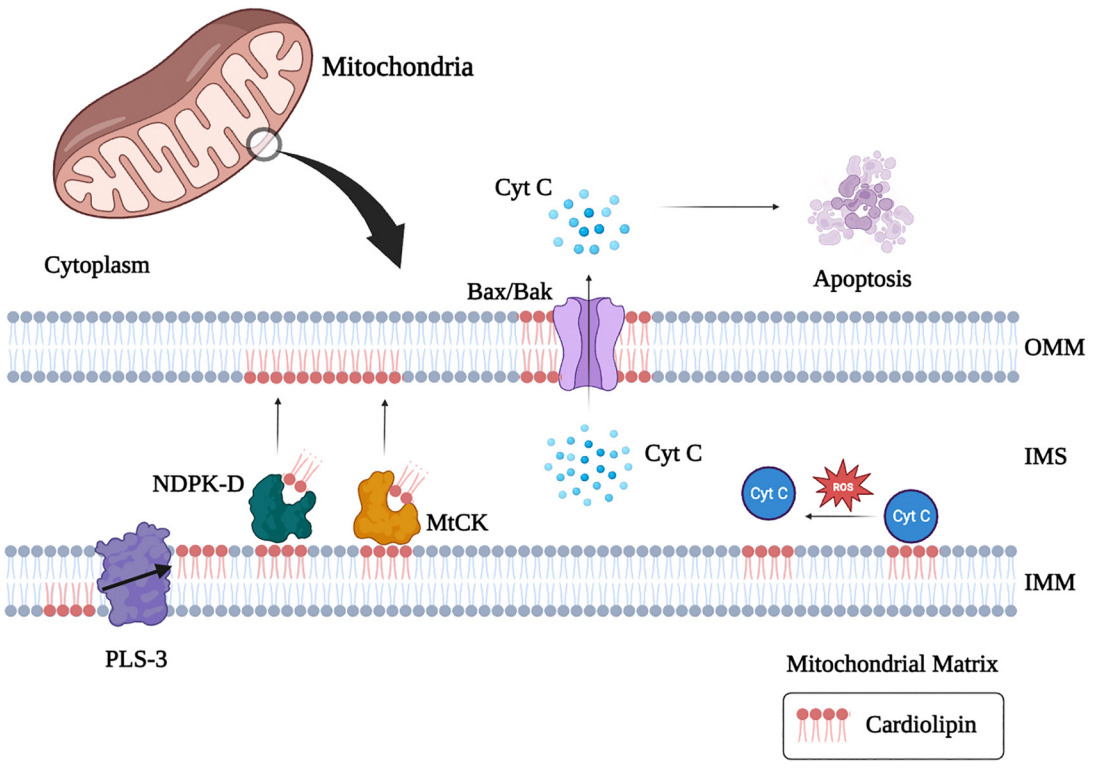
FIGURE 1 ROS-Induced Pathogenesis in DCM and Cardioprotection Through LysoPA



Reactive oxygen species (ROS) generated through dysfunction of electron transport chain in the mitochondria stimulates mitochondrial fission and subsequent apoptosis of cardiomyocytes through different signaling cascades. Lysophosphatidic acids (lysoPA) have been found to contribute in cardioprotection through the activation of mitogen-activated protein kinase phosphatase 1 (MKP1) that intervenes with the phosphorylating activity of different kinases in ROS-induced mitochondrial fission signaling pathway. Created with BioRender. DCM = dilated cardiomyopathy.

PPAR signaling pathway in DCM. Peroxisome proliferator-activated receptors (PPARs) are a group of nuclear receptors comprising of members, namely PPARα, PPARβ/δ, and PPARγ that bind with retinoid X receptor (RXR) as an obligate heterodimer and regulate the gene expression mostly involved in adipogenesis, lipid metabolism, inflammation, and maintenance of metabolic homeostasis.[85] This signaling cascade is initiated by 2 transmembrane proteins, namely CD36 and fatty acid transport proteins (FATP), that play a crucial role in the internalization of some lipid metabolic byproducts, namely oxylipins.[86,87] Oxylipins have been found to alter the myocardial environment in different types of cardiac diseases.[88] As the oxylipins such as 8-hydroxyeicosatetraenoic acid (HETE) and 13-hydroxyoctadecadienoic acid (HODE) are internalized by transmembrane channel proteins such as CD36 and FATP, they first utilize fatty acid binding protein 3 (Fabp3) as a vehicle to get transported to the nucleus where they bind with the intracellular receptors that also act as transcription factors.[89] The binding of 8-HETE and 13-HODE with PPARα and PPARγ, respectively, and further heterodimerization

FIGURE 2 **Dynamics of CL and Cytochrome C in Stressed Myocardium**

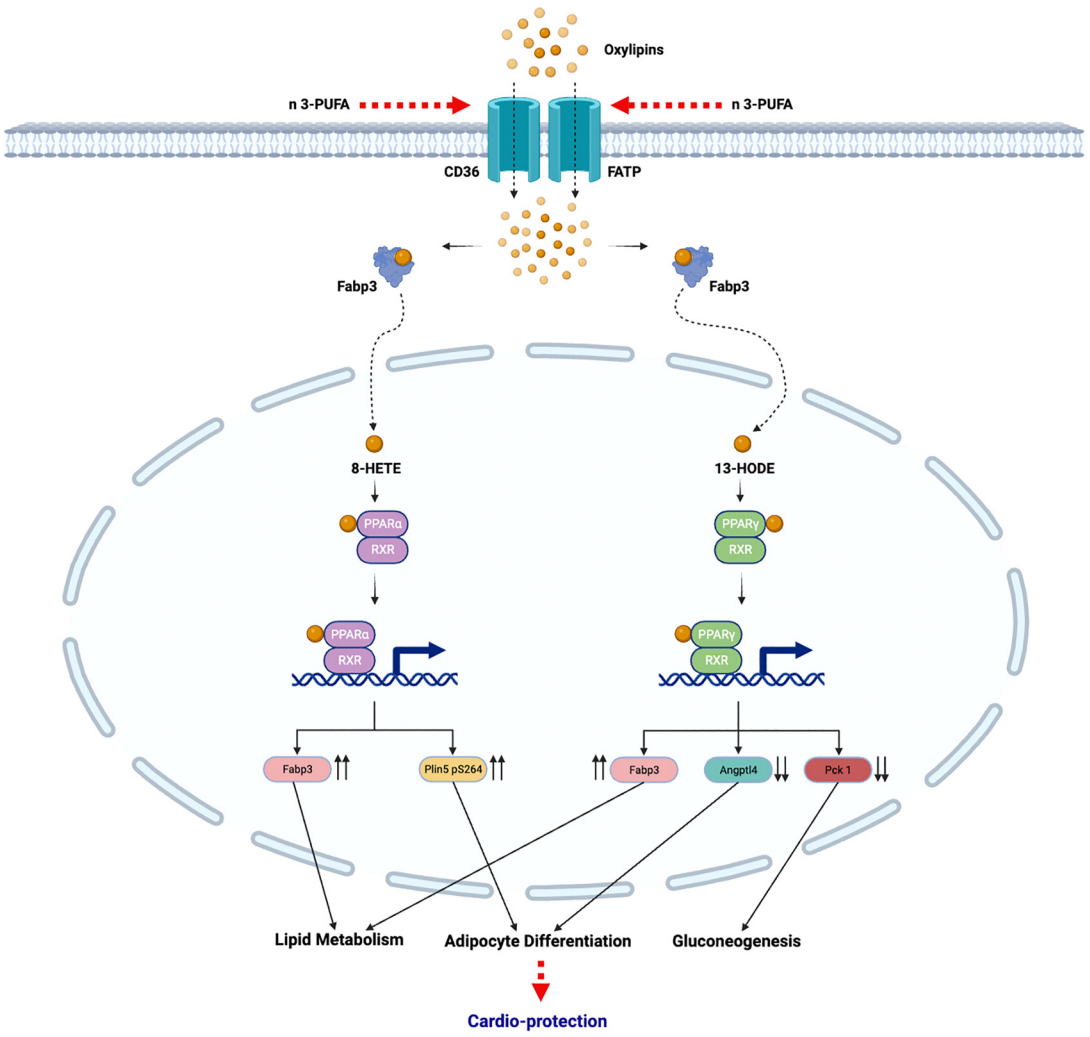


In stressed myocardium, cardiolipin (CL) first flips from the inner leaflet of the inner mitochondrial membrane (IMM) to the outer leaflet and then are carried to the outer mitochondrial membrane (OMM) by mitochondrial creatine kinase (MtCK) and nucleoside diphosphate kinase (NDPK-D). CLs provide room for the incorporation of B-cell lymphoma 2-associated X protein (Bax)/B-cell lymphoma 2 antagonist/killer (Bak), which acts as a channel for the release of cytochrome c (cyt c). The interaction between CLs and cyt c is disrupted due to the peroxidation of fatty acid chains of CL. Created with BioRender.

with RXR, ultimately result in the expression of effector genes such as *Angptl4*, and *Pck1*. These genes are associated with lipid metabolism, adipocyte differentiation, and gluconeogenesis.[90] *Angptl4* is the key regulator of the enzymes lipoprotein lipase that plays a critical role in breaking down fats into triglycerides, whereas *Pck1* encodes an enzyme, namely phosphoenolpyruvate carboxykinase 1, which catalyzes gluconeogenesis.[91] Though there are no pieces of evidence of a direct correlation between the pathogenesis of DCM and gluconeogenesis or fatty acid breakdown, previous works have shown that in a stressed condition, the energy utilization in the cardiac environment is highly dependent on glucose metabolism rather than fatty acid oxidation as in a normal condition.[92] This fact is also supported by the activation of anaerobic processes such as glycolysis in stressed myocardium in order to fulfill the energy need of cardiac cells. This uncoordinated regulation of glucose metabolism and fatty acid oxidation creates an ATP deficit condition in the stressed myocardium that is very much evident in heart failure cases[93] and likely to be similar in the case of DCM.[46] Further, Angiopoietin Like 4 (Angptl4; inhibitor of lipoprotein lipase) and phosphoenolpyruvate carboxykinase 1 (Pck1; first catalytic enzyme of gluconeogenesis) both get up-regulated as a consequence of the alteration of oxylipins in metabolically dysfunctional myocardium.[46] A higher level of PEPCK-1 activity during hypoxic stress conditions is evidently associated with elevated gluconeogenesis to maintain glucose homeostasis in other organs and may also be similar in the myocardium as well during the pathological progression of DCM[93] (**Figure 3**).

Hippo signaling pathway in dilated cardiomyopathy. The Hippo signaling pathway is a signaling cascade that regulates the development of different mammalian organs by controlling cell fate decisions, proliferation,

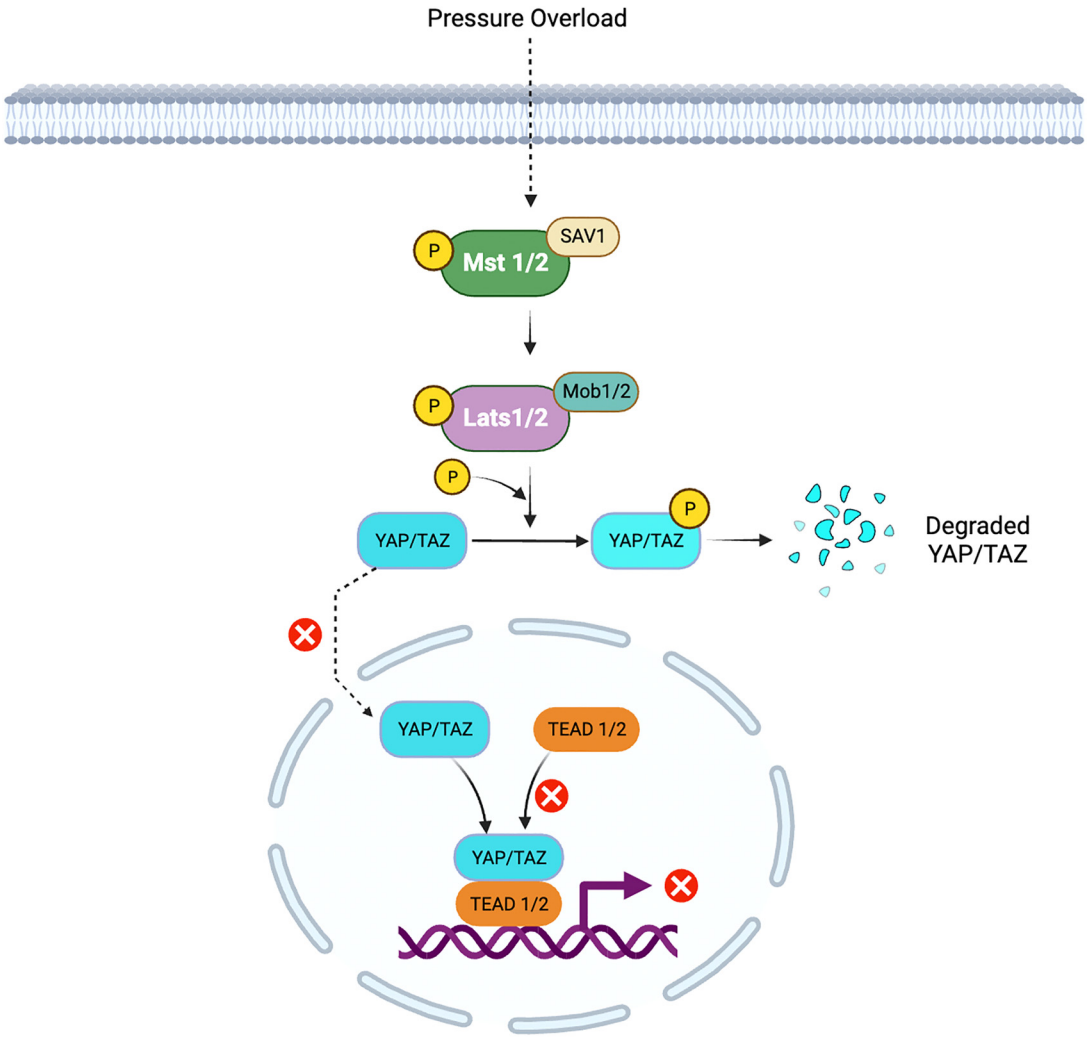
FIGURE 3 DCM Pathogenesis Through PPAR Signaling and Cardioprotective Effect of n-3 PUFA



Oxylipins are some metabolic by-products that modulate lipid metabolism, adipocyte differentiation, and gluconeogenesis in the development of dilated cardiomyopathy (DCM) through the peroxisome proliferator-activated receptors (PPAR) signaling pathway. n-6 polyunsaturated fatty acids (n-6 PUFA), when converted to n-3 polyunsaturated fatty acids (PUFA) in the course of metabolic activity, expression of CD36 and fatty acid transport protein (FATP) is enhanced by n-3 PUFAs. This ultimately results in the channelization of oxylipins inside the cell and subsequent alteration of gene expression related to metabolic activity, thus providing protection to the myocardial environment. Created with BioRender.

and apoptosis. The basic functionality of this pathway is based on the serine-threonine kinase signaling cascade. Several physiological and pathological signals such as cytokines, growth factors, oxidative stress, or myocardial injury can activate this signaling cascade in the heart.[52] The foremost effector molecule of this pathway is a kinase, namely macrophage stimulating protein 1/2 (Mst1/2), which upon activation interacts with an adaptor protein Salvador (Sav1) and phosphorylates downstream proteins such as large tumor suppressor kinase 1 (Lats1/2) and MPS one binder 1/2 (Mob1/2).[94-96] This further promotes the phosphorylation of downstream transcriptional coactivators Yes associated protein (YAP)/transportation analysis zone (TAZ) and facilitates its cytoplasmic retention or proteasomal degradation.[97] On the other hand, the inactivation of upstream kinases ultimately leads to the nuclear translocation of these transcriptional coactivators where they interact with different transcription factors such as TEA domain

FIGURE 4 **DCM Pathophysiological Progression Through Hippo Signaling Pathway**



In the pressure overload condition of the heart, the mitochondrial hippo signaling pathway gets activated to restrict the migration of Yes-associated protein/transcriptional coactivator with PDZ-binding motif (YAP/TAZ) transcription factors. As a result, the expression of some genes associated with cardiomyocyte proliferation and survival gets suppressed, culminating in dilated cardiomyopathy (DCM) phenotypes. Created with BioRender.

transcription factor 1/4 (Tead1/4) and direct the expression of genes associated with cardiac development and cardiomyocyte apoptosis.[98] It has been shown in different studies that components of Hippo-YAP/TAZ signaling, for example, Mst1 and LATS1/2, have been up-regulated in a pressure overload condition in the heart. Moreover, target genes of YAP/TAZ, for example, *Bmp2b*, *Cyr61*, *CTGF*, *miR-152*, *miR-206*, *Oct3/4*, *Park2*, and *Pik3cb*, have been found to significantly contribute to cardiomyocyte proliferation and survival, and to build up resistance against oxidative stress[99] (**Figure 4**). It has been shown that impairment in Hippo signaling ultimately leads to alteration in the mitochondrial lipid constituents (CL, acylcarnitines), which results in disruption of mitochondrial bioenergetics and attenuation in myocardial performance.[53]

CARDIOPROTECTIVE EFFECTS OF LIPIDS. Cardioprotection through lysophosphatidic acids. Wen et al[45] has shown that levels of 4 lysophosphatidic acids (lysoPAs), namely lysoPA 16:0, lysoPA 18:0, lysoPA 18:1, and

JACC: ASIA, VOL. 3, NO. 4, 2023
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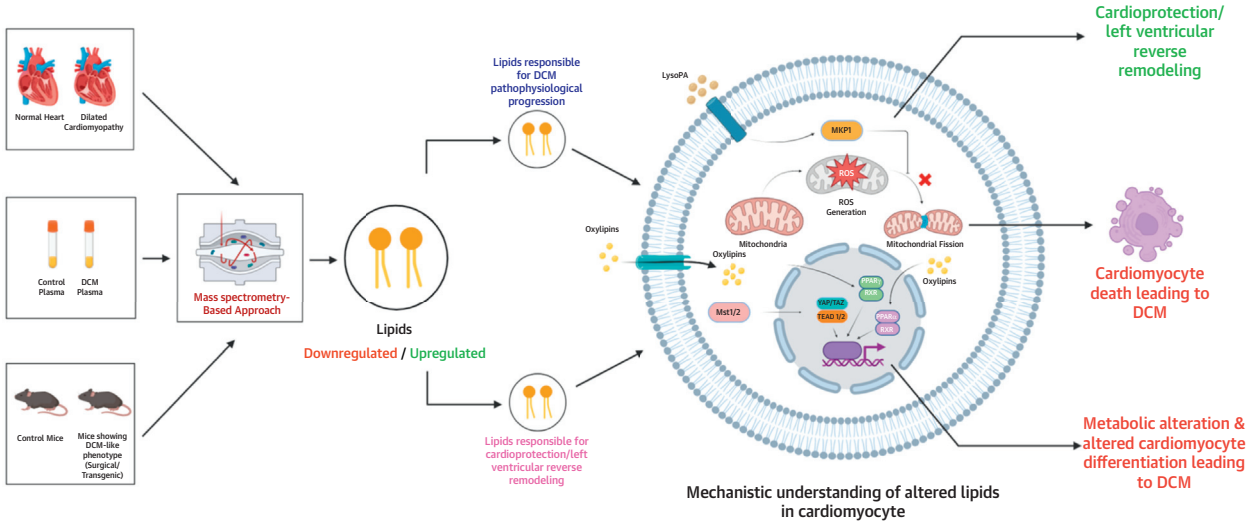
CENTRAL ILLUSTRATION **Mechanistic Role of Altered Lipids in Dilated Cardiomyopathy Pathophysiology and Cardioprotection**



Saha S, et al. JACC: Asia. 2023;3(4):539–555.

The alteration of lipids has been profiled with the mass-spectrometry-based approach in human plasma or serum along with different in vitro and in vivo models of dilated cardiomyopathy (DCM). The lipid molecules modulate the cellular signal transduction in cardiomyocytes to interfere with the metabolic activity and cardiomyocyte differentiation leading to cell death and disease progression of DCM. Specific lipids also play a crucial role in cardioprotection and reverse remodeling of the DCM heart. Created with BioRender. LysoPA = lysophosphatidic acid; ROS = reactive oxygen species.

lysoPA 18:2, have been significantly associated with LVRR in the case of pediatric DCM. The mechanistic background of these lysoPAs has remained elusive. It has been observed that lysoPAs exert their biological effect through high-affinity cell surface G protein-coupled receptors (GPCRs).[100] As lysoPAs bind to GPCR, they activate Ras present downstream of the signaling pathway and further stimulate serial activation of Raf, MEK, and ERK through phosphorylation activity.[101] Upon activation of ERK, they stimulate the expression of MAPK phosphatase 1 (MKP1). Protein phosphatases are 1 of the molecules to contribute in the regulation of MAPK activity. It is known that MKP1 inhibits the p38 MAPK, MEK, and ERK activity that is essential for mitochondrial fission, thus suppressing cardiomyocyte apoptosis by intervening with the proapoptotic factors and protecting the cardiac environment from further decay[102] (Figure 1).

Cardioprotection through intervention in the PPAR signaling cascade. In the study done by Li et al,[46] it has been shown that *Fat1* transgene modulates the PPAR signaling pathway to bring about the cardioprotective effect of n-3 PUFAs. n-3 PUFAs significantly contribute to the up-regulation of the expression of membrane proteins such as CD36 and FATP, which play a crucial role in the internalization of oxylipins. The greater availability of oxylipins for metabolism has significantly altered the gene expression associated with lipid metabolism, adipocyte differentiation, and gluconeogenesis. Significant up-regulation of Fabp3 and perilipin 5 (Plin5), and down-regulation of Angptl4 and Pck1 modulate the metabolic activity that facilitates the cardioprotective function of n-3 PUFAs in a pressure overload condition (Figure 3).

CARDIOPROTECTION THROUGH METABOLIC MODULATORS. DCM leading to heart failure is pathophysiologically associated with neurohormonal imbalance and inflammatory phenotypes that are caused by an increased level of catecholamines, cytokines, and modulation of the renin-angiotensin system.[103] The 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase inhibitors, commonly known as statins, are

found to play a crucial cardioprotective role by mediating anti-inflammatory effect along with improving vascular endothelial function through diminishing the level of tumor necrosis factor (TNF)-α, as well as lipids in the plasma.[104] However, the beneficial effect of statins in non-ICM cases was still to be established. In this scenario, Node et al[105] performed a study in 51 nonischemic DCM patients, of which 24 individuals were treated with simvastatin and 27 individuals received a placebo for 14 weeks. A significant decrease in the serum cholesterol level along with significant improvement in LVEF in patients treated with simvastatin was evidenced. In fact, simvastatin treatment also significantly lowered the plasma concentration of TNF-α, interleukin-6, and B-type natriuretic peptide in patients.[105] In another clinical study, 40 chronic heart failure patients (20 IDC and 20 ischemic DCM) were treated with fluvastatin for 12 weeks. The functional capacity, LVEF, and tissue Doppler mitral annular systolic velocity were improved significantly in participants from both groups (after statin therapy) along with diminished plasma TNF-α and interleukin-6 levels compared with baseline. Significant changes were not evidenced in serum B-type natriuretic peptide and C-reactive protein in this study.[103] The anti-inflammatory effects of statins are brought upon by the inhibition of an array of toll like receptors (TLRs) by statins.[106] Statins interfere with the activity of nuclear factor kappa B (NF-κB) to imply its anti-inflammatory function by two different mechanisms. Firstly, statins interact with TLR4 and subsequently inhibit the TLR4/Myd88/NF-κB signaling cascade.[106] Secondly, statins can also act as inhibitors of MAPK, which mediates the TLR4/Myd88/NF-κB signal transduction.[107,108] NF-κB, in the downstream, acts as a transcription factor and is responsible for the expression of genes such as TNF-α and interleukin 6. Modulation of NF-κB activity through statins thus down-regulates the gene expression of such proinflammatory cytokines and improves cardiac function.[109] These shreds of evidence clearly indicate that short-term statin therapy can play a crucial role in the improvement of cardiac functions associated with DCM. However, the latest guidelines for treating DCM by the American College of Cardiology recommend the utilization of drugs such as angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta-blockers, aldosterone antagonists, and sodium-glucose transporter 2 inhibitors for the treatment of DCM and does not include statin therapy.[15,110]

HIGHLIGHTS

- DCM is a type of cardiomyopathy, pathophysiologically characterized by ventricular dilatation and systolic dysfunction.
- Lipids are the major source of energy for the heart. Perturbation in the lipidome can lead to the pathological progression of DCM.
- Lipid alteration mainly affects the mitochondrial dynamics during DCM progression.
- Mass-spectrometry-based lipidomics approach is essential and key to deciphering DCM-specific lipid signatures for understanding the disease mechanism and discovering better diagnostic biomarkers.

CONCLUSIONS

Understanding the causes and/or contributing factors in initiating and progressing of myocardial systolic dysfunction in patients with ICD always remains an enigma. The abnormal myocardial energy metabolism may be the trigger for depressed myocardial contractility due to the state of energy depletion. Lipids are the major substrate source of myocardial energy demand. The alterations in fat metabolism may play a critical role in the pathogenesis of DCM. Thus, a comprehensive analysis of levels of different fatty acids, other lipid fractions, and their metabolic byproducts in DCM patients may provide some clues about key alterations in lipid metabolism in failing hearts. Classically, HDL or LDL can be associated with varied kinds of metabolic diseases along with cardiovascular diseases. Thus evaluating the levels of HDL and LDL alteration solely cannot be utilized as specific markers for DCM.[111] In fact, evidence shows that in very long-chain acyl-CoA dehydrogenase–null mice fed with a high-fat diet also presented with prolonged QT interval, accumulation of TGs, along with down-regulation of docosahexaenoic acid in the myocardium.[112] These pieces of evidence indicate that there may be some overlaps with the specifically altered lipid signatures of DCM and other forms of cardiovascular diseases. Thus, harnessing the advantage of the MS-driven lipidomics approach in the characterization of lipid species to elucidate disease-

specific lipid markers with more specificity and sensitivity in discriminating DCM is essential. This omics-based approach utilizes high-throughput MS-based techniques to have a greater insight into the pathophysiological alterations in DCM. These techniques mostly exploit the quantitative alterations of proteins, small metabolites, and lipids to give a comprehensive idea about the disease-specific etiologies, thus providing more specificity and sensitivity. This opens a new window of opportunity to explore newer treatment targets and help in the understanding of derangements in the metabolic pathways contributing to the development of systolic heart failure. In this review, we have summarized such studies that are based on lipidomic alterations in DCM patients. All the studies related to human serum or plasma samples and in vivo and in vitro model systems have been included to provide critical insights into the current status of global lipidomic-based clinical research associated with DCM. Though most of the studies have been done with a targeted approach, it is now imperative to perform a global lipidomic assessment to discover a panel of a biomarker that will impart a great diagnostic and prognostic value. Moreover, the biomolecular mechanistic interventions of most of these lipids in DCM are yet to be explored. Thus, it is essential to perform comprehensive plasma lipidomic analysis with a next-generation mass spectrometry-based approach integrated with molecular biology approaches to propose a panel of lipid biomarkers of DCM and provide critical mechanistic insight into DCM (**Central Illustration**).

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The Indian Council of Medical Research (ICMR) funded this study (Dr Basak). Mr Saha is supported by a HTRA doctoral program fellowship (MHRD, Government of India). All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Trayambak Basak, School of Biosciences and Bioengineering, BioX Center, IIT-Mandi, Kamand Campus, Mandi-Bajaura Road, Himachal Pradesh 175075, India. E-mail: trayambak@iitmandi.ac.in.

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KEY WORDS **dilated cardiomyopathy, heart failure, lipidomics, mass spectrometry, mitochondrial dysfunction**