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UNIVERSITY OF CALIFORNIA SAN DIEGO

Deletion of Tafazzin in Cardiomyocytes Results in Dilated Cardiomyopathy

A Thesis submitted in partial satisfaction of the requirements for the degree Master of Science

in

Biology

by

Mason Zhu

Committee in charge:

Professor Ju Chen, Chair
Professor Eric Allen, Co-Chair
Professor Yimin Zou

2020

The Thesis of Mason Zhu is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

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Co-Chair

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Chair

University of California San Diego

2020

DEDICATION

I dedicate this thesis to my incredible parents and sister, who have time and time again given me unconditional support and never-ending love. Without them, I wouldn’t be able to be the proud person I am today. Their sacrifices have given my life meaning and I hope to make them proud, every day.

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LIST OF ABBREVIATIONS

BTHS: Barth syndrome

CL: cardiolipin

MLCL: monolyso-cardiolipin

TAZ: Tafazzin

CKO: cardiomyocyte-specific knockout

XMLC2: Xenopus leavis myosin light-chain 2

DCM: dilated cardiomyopathy

Anf: atrial natriuretic factor

Bnp: B-type natriuretic peptide

Coll1a1: collagen, type I, alpha I protein

Coll3a1: collagen, type III, alpha I protein

LVIDd: left ventricular internal diameter at end-diastole

LVIDs: left ventricular internal diameter at end-systole

FS: fractional shortening

qRT-PCR: quantitative reverse transcription polymerase chain reaction

PA: phosphatidic acid

CDP-DAG: cytidine diphosphate diacylglycerol

PGP: phosphatidylglycerolphosphate

PG: phosphatidylglycerol

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My genuine appreciation also goes to Eric Allen and Yimin Zou for the time and effort they invested to be on my committee. Moreover, I would like to thank them for being exceptional educators and mentors who are truly dedicated to the learning community at UC San Diego. I am grateful for the privilege to learn from and interact with students under their instruction. Their influence has not only imparted upon me the importance of teaching and mentoring students but also enabled me to experience the rewards firsthand.

In conclusion, I would like to thank Xi Fang, Ze'e Chen, Siting Zhu, and Changming Tan for everything they have taught me about molecular cardiology research and beyond. Through their guidance and genius, I learned what scientific inquiry is about and have been able to independently think about science. I am forever grateful for their guidance and patience with teaching me science.

ABSTRACT OF THE THESIS

Deletion of Tafazzin in Cardiomyocytes Results in Dilated Cardiomyopathy

by

Mason Zhu

Master of Science in Biology

University of California San Diego, 2020

Professor Ju Chen, Chair
Professor Eric Allen, Co-Chair

Cardiolipin, the signature phospholipid of mitochondria, is crucial for mitochondrial function and architecture in the heart. Defects in cardiolipin remodeling processes and metabolism lead to cardiomyopathy, as seen in patients with Barth Syndrome (BTHS). Tafazzin is a major acyltransferase in CL remodeling that transfers linoleoyl groups to monolyso-CL until the final symmetric acyl composition is achieved. Mutations in Taz that result in BTHS cause inefficient transacylation between phosphoplipid-lysophospholipids, leading to cardiomyopathy. However, little is known as to the detailed molecular mechanisms by which Taz deficiency and

consequent CL absnormalities lead to the progression of cardiomyopathy. In our present study, we found that loss of Tafazzin results in increased levels of cardiac stress markers, Anf and Bnp. Histological analysis demonstrated that mice with Taz deletions had thinner left ventricular walls and dilated left ventricular chambers relative to the control mice. Echocardiography analysis also showed that loss of Tafazzin causes decreased cardiac function. Together, these observations suggest that deletion of Tafazzin in cardiomyocytes results in dilated cardiomyopathy as seen in Barth Syndrome.

INTRODUCTION

The function of cardiac mitochondria:

Mitochondria are organelles in the body that generate most of the chemical energy to power the cell's biochemical processes. Mitochondria are highly present in cardiac cells because of high energy demands in the heart and has a vital function of producing over 90% of the ATP required for normal cardiac function through oxidative phosphorylation processes (1-3). Cardiac mitochondria are also involved in the regulation of amino acid metabolism, and lipid, iron, and calcium homeostasis. The architecture of the mitochondria lends itself to the diversity of functions it serves because of the complex double membrane structure; mitochondrial fission, fusion, and mitophagy are some of the processes that are tightly regulated by this complex molecular machinery (4-6). Mutations in genes encoding mitochondrial proteins are frequently associated with human cardiomyopathies (7, 8).

The function and biosynthesis of cardiolipin in cardiac mitochondria:

Cardiolipin (CL) is exclusively found in mitochondrial membranes and comprises up to 20% of the total phospholipid content in mitochondria, making it the trademark phospholipid in mitochondria (9, 10). CL is unlike other phospholipids, because it contains four fatty acyl chains rather than two fatty acyl chains connected by two phosphatidyl moieties bridged by glycerol (Figure 1). CL in the mammalian heart has a defined lipid composition of linoleic acid (18:2) as the predominant form of fatty acyl chain in all four chains, forming the highly symmetric tetralinoleoyl-CL (11, 12) (Figure 1). CL plays an essential role in mitochondrial functions, including mitochondrial membrane architecture reorganization (13, 14), mitochondrial fusion and fission (15-18), mitophagy (19, 20), oxidative phosphorylation and bioenergetics (21-26),

and regulation of apoptosis processes (27-29).

CL biosynthesis occurs exclusively in the mitochondria, as opposed to most membrane lipids in the mitochondria that are synthesized in the endoplasmic reticulum (ER) and then transported into the mitochondria. The biosynthesis of CL is a highly conserved biopathway through various model organisms like yeast and mammals (30). The *de novo* synthesis of CL starts from phosphatidic acid (PA) and is catalyzed by a series of enzymes to eventually form nascent CL (unremodeled CL), which contains two phosphatidyl groups that are linked by a glycerol molecule (Figure 2) (31-36). Nascent CL contains a mixture of acyl chain lengths and degrees of unsaturation because the enzymes involved in *de novo* CL biosynthesis do not demonstrate any acyl specificity (30, 37, 38).

CL remodeling (also called maturation) processes are defined by removal and replacement of acyl chains with other acyl chains. This process is essential to generating the mature CL that is symmetric and has the final acyl composition of four linoleoyl-groups (C18:2) in the heart (Figure 1) (39). This deacylation-reacylation process is also called the Lands cycle. The initial process in the Lands cycle consists deacylation of the nascent CL by phospholipases by removing the saturated fatty acyl chains from CL, forming the intermediate monolyso-CL (MLCL), with only 3 fatty acyl chains (40-42). The reacylation step involves a specific acyl group from other phospholipids being transferred to MLCL by acyltransferases or transacylases, forming a remodeled fatty acyl chain. CL goes through multiple cycles of this deacylation-reacylation process to achieve the final composition of four linoleoyl-groups attached (Figure 2)

(37, 43, 44).

Mutations in Tafazzin disrupt CL remodeling:

Tafazzin (TAZ) (12, 41, 45-47) is an enzyme, among MLCL acyltransferase 1 (MLCLAT1) (48-50) and acyl-CoA:lysocardiolipin acyltransferase-1 (ALCAT1) (51), that functions to reacylate MLCL (52). Mutations in Taz cause BTHS (53, 54), suggesting that Taz is an essential acyltransferase in the cardiolipin remodeling process. TAZ deficiency in BTHS patients results in inefficient transacylation between phospholipid-lysophospholipid. This in turn will significantly reduce the incorporation of linoleoyl-groups into CL (55), leading to accumulated levels of MLCL and decreased levels of mature CL. This accumulation of MLCL and the lack of reacylation of MLCL leads to the degradation of nascent CL (12). Cardiolipin biosynthesis activity remains normal in BTHS patients (47). These defects caused by mutations in Tafazzin will lead to lower CL concentration, abnormal fatty acyl composition in CL, and an increased MLCL:CL ratio (Figure 2) (12, 47, 56-59).

Barth Syndrome and Tafazzin:

BTHS is a cardiac and skeletal mitochondrial myopathy that is passed through X-linked inheritance patters (60-62). Patients with BTHS will exhibit a variety of clinical features, such as skeletal muscle weakness, neutropenia, growth retardation, and cardiomyopathy (60-62). Many of those affected will die in early stages of infancy or childhood, but those who survive can live up to their late forties (60-64). Cardiomyopathy is the most prevalent cause of death in BTHS patients. Most cases are dilated cardiomyopathy (DCM), but there are also cases of hypertrophic

cardiomyopathy, endocardial fibroelastosis, and left ventricular non-compaction, among many other cardiomyopathic features. Cardiomyopathies in BTHS are highly prevalent in the earliest stages of life, most often BTHS patients being diagnosed in their first year (63). Treatments have included heart transplants in 14% of BTHS patients (63). Biopsies of the heart of BTHS patients reveals many mitochondrial structural malformations and dysfunctions, including disorganized distribution, abnormal sizes, and tightly stacked or circular bundles of cristae (60, 61, 63, 65). However, little is still known to the underlying molecular mechanism of BTHS and there is still no curative therapy for the cardiomyopathy of BTHS patients.

The majority of BTHS studies have utilized other non-mammalian organisms such as yeast (43), Drosophila (66), Zebrafish (67), cultured cells (47), or a doxycycline induced-short hairpin RNA TAZ knockdown (KD) mouse (68-71). Most likely due to the incomplete deletion of the TAZ protein, TAZ KD mice displayed mild disease phenotypes (68). Thus, a Taz knock-out mouse model is essential to the understanding of the molecular basis underlying the cardiomyopathy caused by deletion of Taz.

In this study, I am going to investigate the role of TAZ in cardiac function by analyzing Taz cardiomyocyte-specific knockout (cKO) mice. We hypothesize that TAZ does play an essential role in maintaining normal CM function.

MATERIALS AND METHODS

Animal protocol and consent

The UCSD animal care personnel maintained all the animals in vivarium of the Biomedical Research Facility II in the UCSD School of Medicine. Mice were maintained and enriched in standard dark/light cycle protocols for animal care. Standard requirements for rodents in the Institutional Animal Care and Use Committee (IACUC) guidelines were maintained, keeping at most five individuals per cage. The IACUC at the University of California San Diego approved all experimental procedures. UCSD has an Animal Welfare Assurance document (A3033-01) on file with the Office of Laboratory Animal Welfare and is fully accredited by the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) International.

Mouse models

We utilized CRISPR/Cas 9 technology to generate a floxed Taz mouse line in which exons 5 to 10 of Taz were flanked by two loxP sites to (Figure 3). Homozygous floxed TAZ mice were viable and born at expected Mendelian ratios with no observed defects. Cardiomyocyte-specific Taz knockouts (cKOs) were successfully generated by crossing floxed Taz mice to Xenopus leavis myosin light-chain 2 (Xmlc2)-Cre transgenic mice (72, 73), which is used to subside specific gened in developing CMs from embryonic day (E)7.5, and has been demonstrated to have no cardiac toxicity (73). Genotyping was performed as detailed in previous publication with primers indicated in Table 1 (74). (Taz cKO mice were born at Mendelian ratios and survived to adulthood with body weights comparable to the Cre negative control mice.

Animal procedures and echocardiography

Before performing the echocardiographic study, all of the mice were anesthetized with 1% isoflurane. The echocardiography was performed using a FUJIFILM VisualSonics SonoSite Vevo 2100 ultrasound system with a 32- to 55-MHz linear transducer. Because fractional shortening (FS) is a reliable indicator of cardiac function, the percentage of FS was used as an indicator of systolic cardiac function. Echocardiographic measurements also included heart rate (HR), end-diastolic left ventricular internal diameters (LVIDd), and end-systolic left ventricular diameters (LVIDs), LV posterior wall thickness (LVPWd). LVIDs and LVIDd were determined from the LV M-mode tracing.

Histology

Heart tissue samples were isolated from sex- and age-matched littermates. Mouse hearts were washed in a PBS solution before being fixed overnight in 4% paraformaldehyde. Dehydration of the mouse hearts were performed in 70% ethanol. The dehydrated hearts were fixed in paraffin and sliced into 10-µm thickness coronal sections. The sections were stained with Masson's trichrome and Hematoxylin and Eosin and then imaged. The Hamamatsu NanoZoomer2.0HT Slide Scanning System imaging device was sued to image the prepared heart sections for analysis.

Quantitative RT-PCR

We extracted total RNA from mouse left ventricles using a TRIzol reagent (Life Technologies, Thermo Fisher Scientific) according to the appropriate levels as specified by

protocol and user manual by the manufacturer. Reverse transcription was facilitated by the MMLV Reverse Trascriptase (Bio-Rad). Primer sequences for the quantitative RT-PCR (qRT-PCR) are complimentary to the respective DNA sequence of the analyzed proteins. Primer sequences are found in Table 1. We used the SsoFast EvaGreen Real-Time PCR Master Mix (Bio-Rad) to perform RT-PCR reactions in 96-well PCR plates in the Bio-Rade CFX96 Thermocycler.

Statistical analysis

Data distribution was assumed to be normal. Microsoft Excel was used to analyze data and all the error bars shown in the figures are s.e.m. We used the GraphPad Prism v6 (GraphPad Software Inc., La Jolla, CA) to perform statistical analyses of our data.

RESULTS

Generation of Taz cardiomyocyte-specific constitutive knockout (cKO) mice

The floxed Taz mouse line was generated in which exons 5 to exons 10 of Taz were flanked with two loxP sites (Figure 2) by utilizing CRISPR/Cas 9 techniques (138). Hemizygous Taz cKO male mice ($Taz^{F/Y}$; Cre+) were generated by crossing female floxed Taz mice to Xmlc2-Cre ($Taz^{+/Y}$; Cre-) male mice. The hemizygous Taz cKO male mice are allowed to survive to adulthood so the hemizygous *Taz* cKO male mice ($Taz^{F/Y}$; Cre+) can cross with heterozygous floxed *Taz* female ($Taz^{F/+}$; Cre+) to generate cardiomyocyte-specific Taz knockout (cKOs) mice. Quantiative PCR (qPCR) analysis reveals successful knockout and diminished expression of Taz in the Taz cKO mice compared to the controls at 2 months and 4 months of age (Figure 3).

Taz cKO mice exhibit increased levels of cardiac stress

Preliminary data showed that all of the Taz cKO mice developed DCM at 4 months of age. Cardiac physiological studies were used to assess the long-term effects caused by the loss of TAZ in cardiomyoocytes starting at 1 month of age. The ratio of the heart weight to body weight and heart weight to tibia length were also measured at the specific ages described above.

Cardiac fetal gene markers, atrial natriuretic factor, and B-type natriuretic peptide, as well as pro-fibrotic genes, collagen α1 types I and III, were assessed by qRT-PCR analysis to evaluate the molecular evidence of cardiac stress and fibrosis. qRT-PCR analysis of cardiac fetal gene markers, atrial natriuretic factor (Anf) and B-type natriuretic peptide (Bnp), revealed elevated cardiac stress in Taz cKO hearts compared to controls at 2 months of age (Figure 4A).

We also measured the expression levels of these markers at 4 months of age as well and continued to see elevated expression of Anf and Bnp in Taz cKO hearts compared to controls (Figure 4B). However, pro-fibrotic genes, collagen α1 types I and III, did not show any significant change in expression levels between Taz cKO hearts and control hearts at both 2 months and 4 months of age.

Taz deletion causes dilated cardiomyopathy

Histological and morphological analyses of Taz cKO mice and controls were performed to elucidate the structural and functional changes due to deletion of Taz. Histological analysis showed thinner left ventricular (LV) walls and dilated LV chambers at 4 and 6 months of age in mutants relative to controls (Figure 2D). Echocardiographic measurements further confirmed a dilated cardiomyopathy (DCM) phenotype in the Taz cKO mice, with decreased fractional shortening (FS). Approximately 20% of the cKO mice developed severe DCM at 2 months of age, and at 4 months of age, all of the cKO mice exhibited severe DCM phenotypes (Figure 6). Echocardiographic analysis of the end-diastolic left ventricular internal diameter (LVIDd) and end-systolic left ventricular internal diameter (LVIDs) revealed a significant increase in diameter in both male and female Taz cKO mice at 4 months of age, while not seeing a significant change at 2 months (Figure 6C, 6D). Consistent with histological observations, these findings suggest that deletion of Taz results in dilated cardiomyopathy.

DISCUSSION

TAZ plays an essential role in the maintenance of normal cardiac function. An essential component of the cardiolipin remodeling process in the mitochondria of cardiomyocytes, TAZ participates in the reacylation step of the Lands cycle in cardiolipin remodeling to form the highly symmetric mature tetralinoleoyl-CL (18:2). Mutations and even downregulation of Taz have been reported to lead to dilated cardiomyopathy and heart failure in numerous patient cases. Although it has been shown that mutations of Tafazzin in human patients leads to development of dilated cardiomyopathy and a progressive loss of cardiac and skeletal function, little is known to the exact molecular mechanism by which the increased levels of MLCL and decreased levels of nascent and mature CL lead to the progression of cardiomyopathy.

Our present study uses knockout mice to elucidate the effect that Taz knockout in mice has on cardiac function and structure. We performed a comprehensive time course of the cardiac physiological studies to assess the long-term effects of Taz cKO on cardiac function in the Taz cKO mice, compared to littermate controls. Heart weight to body weight and heart weight to tibia length ratios were also measured and analyzed; there were no significant differences between the Taz cKO mice compared with the controls. The expression levels of the cardiac fetal gene markers, Anf and Bnp, were both significantly increased in the Taz cKO mice at 2 and 4 months of age. The profibrotic genes were within the normal limits compared to that of the control mice at 2 and 4 months of age. Furthermore, histological analysis revealed that the

mutant hearts exhibited thinner LV walls and dilated LV chambers at 4 and 6 months of age in mutants relative to controls. The echocardiographic analyses confirmed this DCM phenotype, showing significantly decreased fractional shortening, end-diastolic left ventricular internal diameter (LVIDd), and end-systolic left ventricular internal diameter (LVIDs) in the Taz cKO mice at 4 months of age. Interestingly, the same observations were not observed for mice at 2 months of age. As mice are generally considered mature adults between 3 to 6 months, it brings up a question why DCM phenotypes are not observed during development stages, but seen later in adulthood. Together, our data suggest that the Taz knockout leads to dilated cardiomyopathy and that TAZ does play an essential role in maintaining normal CM function and structure.

Mitochondrial functions are inextricably linked to their cellular organization, size, morphology, membrane structure, fusion and fission processes, as well as mitophagy (70-72). Electron micrographs of cardiac muscle biopsies from BTHS patients reveals severe DCM and structural defects in the mitochondria, like abnormal size, disorganized distribution, and tightly stacked bundles of cristae. Since Taz participates in the process of cardiolipin remodeling in the mitochondria of cardiomyocytes, mitochondrial defects should be analyzed. Mitochondrial respiration defects using isolated mitochondria from Taz cKO and control hearts of mice at 4 months of age should be performed to investigate whether loss of TAZ reduces mitochondrial respiration. Protein levels of the oxidative phosphorylation complex (OXPHOX) should also be analyzed to investigate whether these OXPHOS complexes are affected in function in Taz cKO hearts.

In conclusion, our results demonstrated that Taz is essential for cardiac function. In future study, we will analyze the detail molecular in which by which Taz deficiency and consequent CL abnormalities lead to the progression of DCM. Our Taz cKO mouse also provides us with a unique model to investigate these potential therapeutic approaches for BTHS cardiomyopathy.

FIGURES

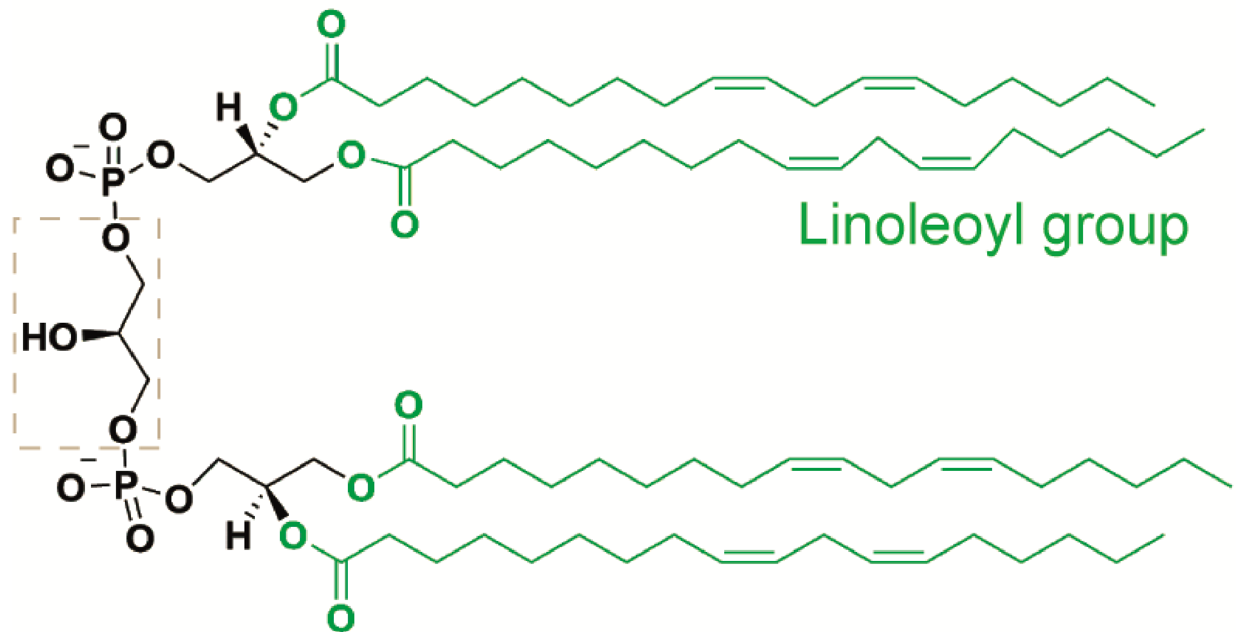

Figure 1. **The mature cardiolipin (CL).** Tetralinoleoyl-CL. In green: linoleoyl group.

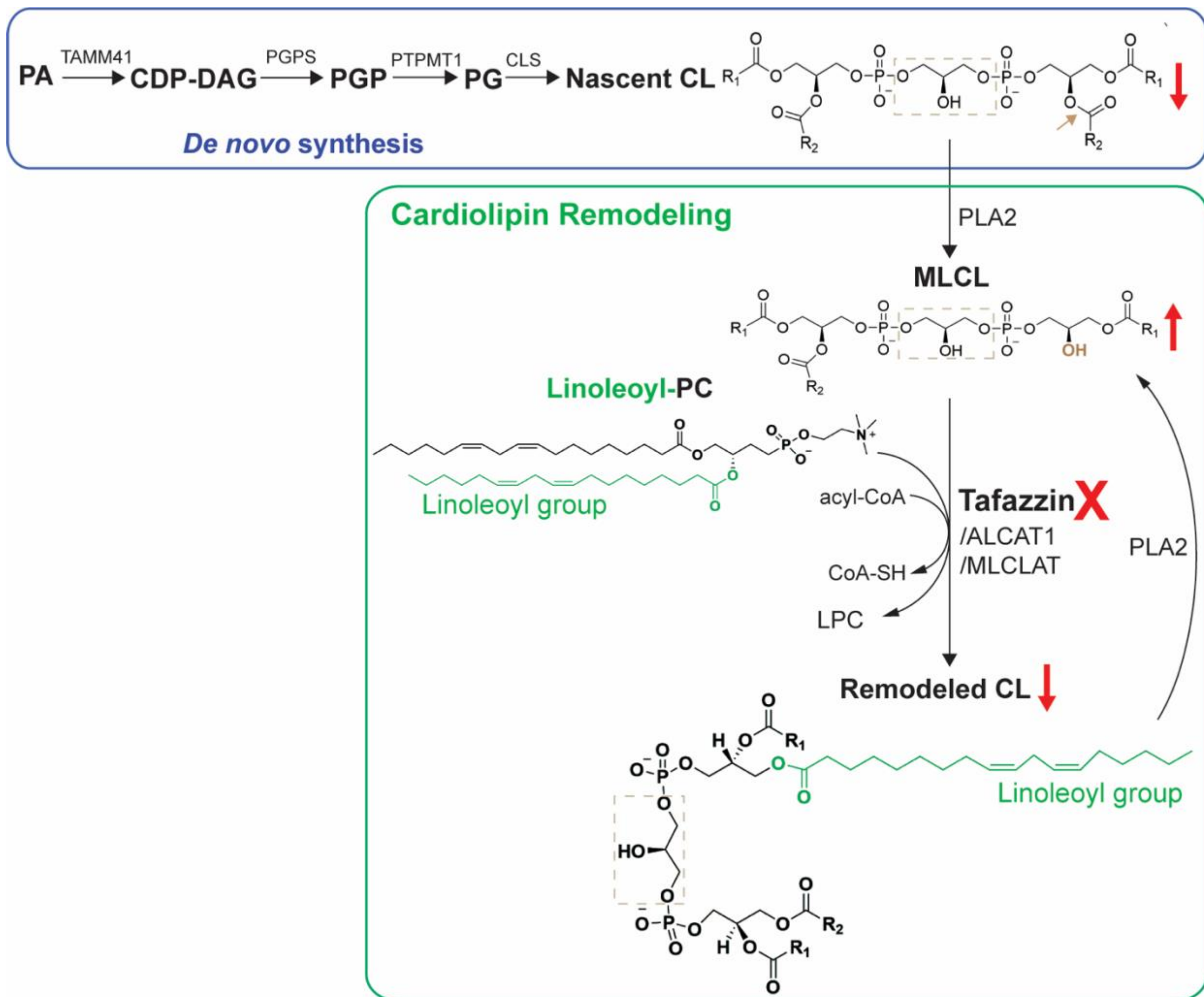

Figure 2. **The biosynthesis pathway for mature cardiolipin (CL).** CL de novo synthesis and remodeling (green box) in mitochondria. backbone. PA: phosphatidic acid; CDP-DAG: CDP-diacylglycerol; PGP: phosphatidylglycerolphosphate; PG: phosphatidylglycerol; TAMM41: TAM41 Mitochondrial translocator assembly and maintenance homolog; PGPS: phosphatidylglycerol phosphate synthase; PTPMT1: Protein Tyrosine Phosphatase Mitochondrial 1; CLS: CL synthase. iPLA2: Calcium-independent phospholipase A2; PC: phosphocholine; LPC: lysophosphocholine; ALCAT1: acyl-CoA:lysocardiolipin acyltransferase-1; MLCLAT: monolyso-CL acyltransferase 1. Red arrows: changes in BTHS patients.

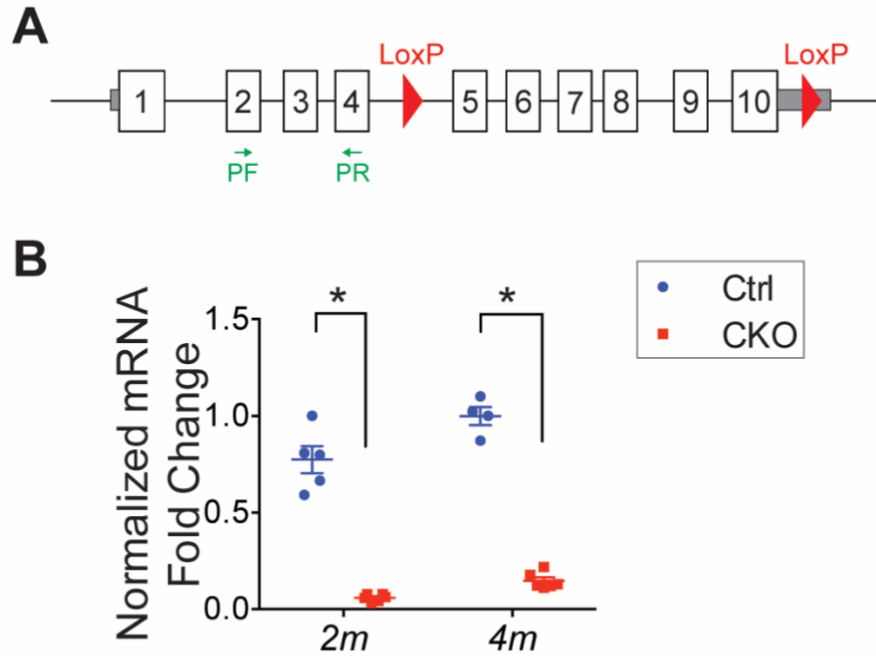

Figure 3. **Taz cardiomyocyte-specific knockout (cKO) mice develop DCM.** (A) Targeting strategy of Taz floxed mice; Two loxP sites (red) flanking exons 5-10 of Taz were inserted by utilizing CRISPR/Cas9 technology. Gray box: 5'UTR and 3'UTR. The locations of the primers used for quantitative PCR (qPCR) are indicated by green arrows. (B) qRT-PCR analysis revealed successful knockout and diminished expression of Taz in the Taz cKO mice at 2 and 4 months of age.

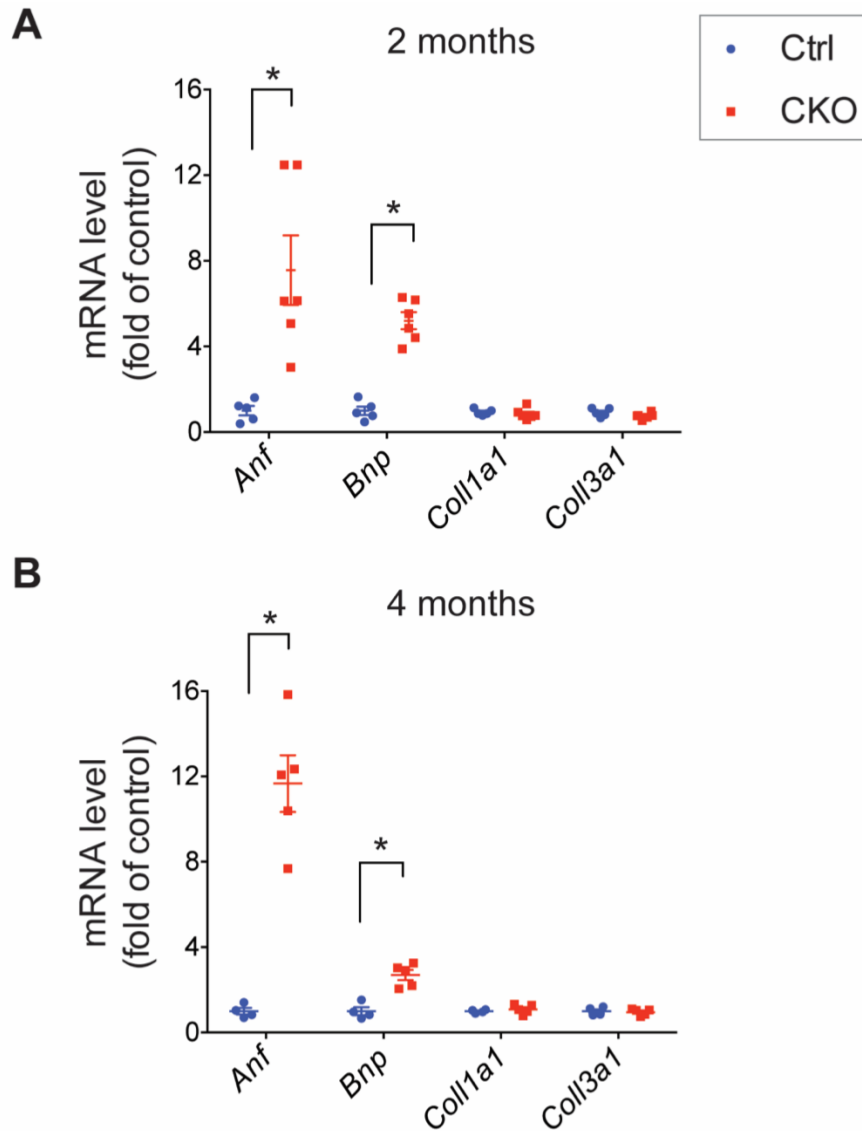

Figure 4. **Taz cardiomyocyte-specific knockout (cKO) leads to increased expression of cardiac stress markers but not profibrotic markers**. **(A-B)** qRT-PCR analysis revealed elevated levels of cardiac stress markers atrial natriuretic factor (Anf) and B-type natriuretic peptide (Bnp), and no change in fibrosis markers Coll1a1 and Coll3a1, in hearts of Taz cKO mice compared to control mice at 2 **(A)** and 4 **(B)** months of age.

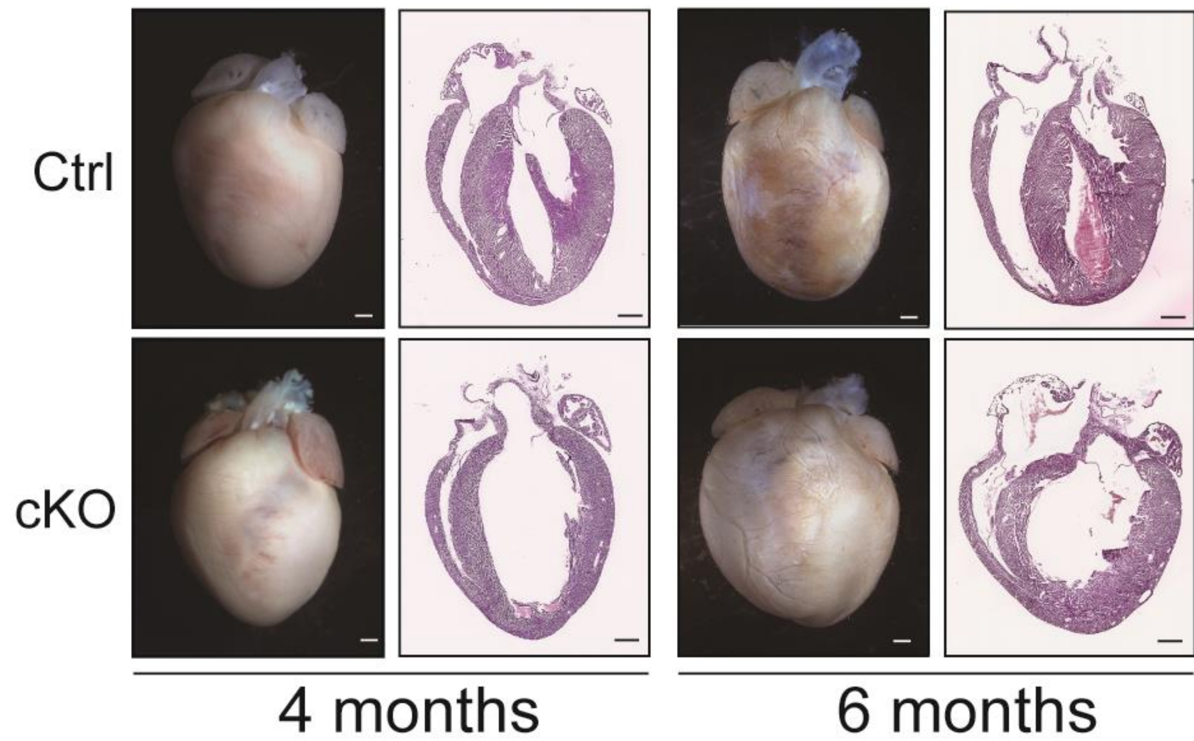

Figure 5. **Whole mouse hearts (left) and Hematoxylin and Eosin-stained sections (right) from Taz cKO and control mice.** Histological analysis showed thinner left ventricular (LV) walls and dilated LV chambers at 4 and 6 months of age in mutants relative to controls.

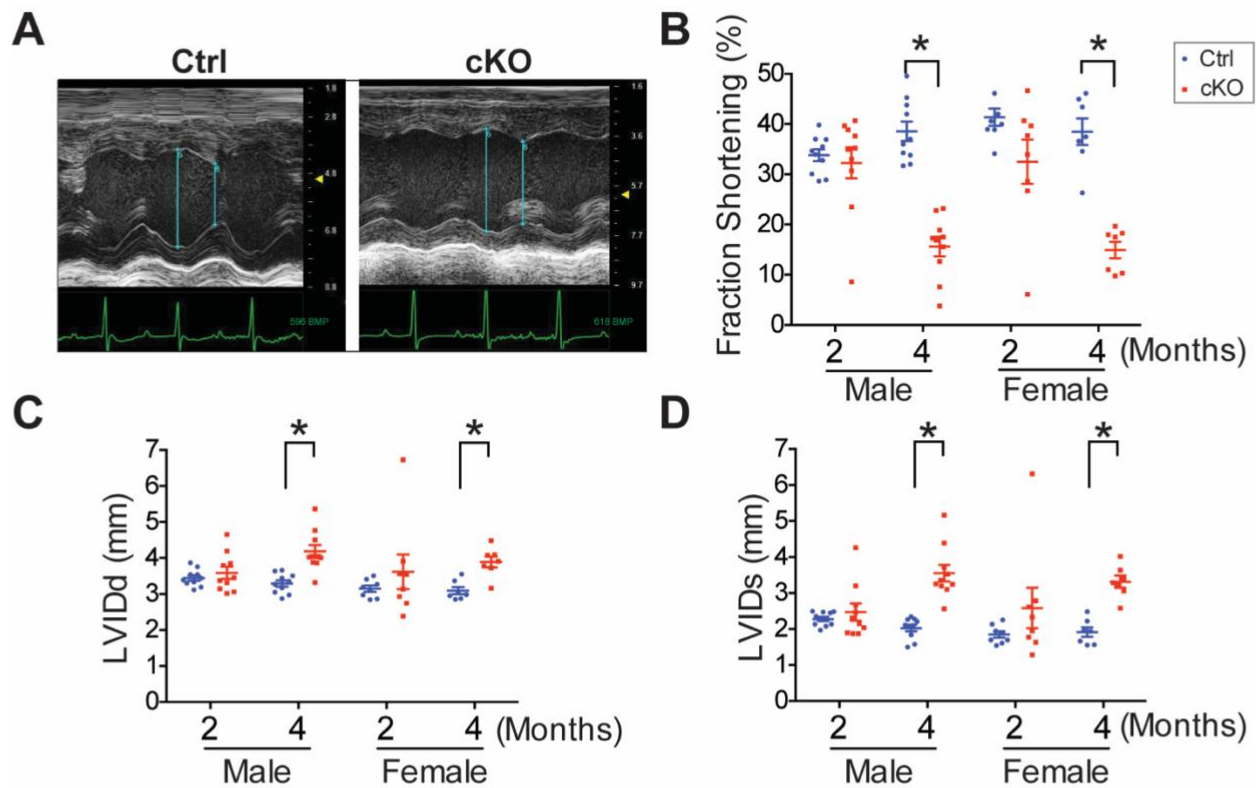

Figure 6. **Echocardiography analysis revealed DCM phenotypes in Taz cKO mice. (A)** Representative echocardiographic images from control and cKO mice at 4 months; **(B-D)** Echocardiography analysis of cardiac structure and function at 2 and 4 months by **(B)** fractional shortening (FS), left ventricular internal diameter at **(C)** end-diastole (LVIDd) and **(D)** end-systole (LVIDs). N=7-10 per group *P<0.05.

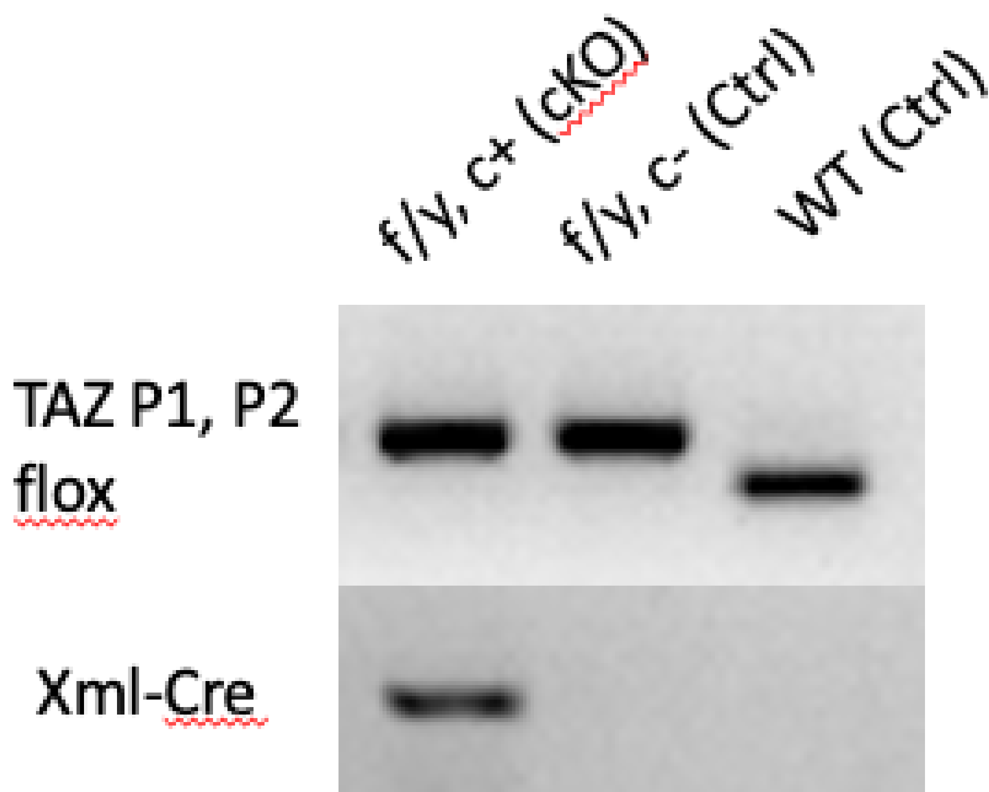

Figure 7. **Genotyping results of Taz cKO mice.** The TAZ cKO mice successfully express the Cre recombinase. Xml-Cre: Xenopus laevis strain expressing Cre recombinase.

TABLES

Table 1. Primer List

Gene	Forward	Reverse
ANF	GATAGATGAAGGCAGGAAGCCGC	AGGATTGGAGCCCAGAGTGGACTAGG
BNP	TGTTTCTGCTTTTCCTTTATCTGTC	CTCCGACTTTTCTCTTATCAGCTC
Collagen 1a1	TCACCAAACTCAGAAGATGTAGGA	GACCAGGAGGACCAGGAAG
Collagen 3a1	ACAGCAGTCCAACGTAGATGAAT	TCACAGATTATGTCATCGCAAAG
TAZ P1, P2	GAGGTAGGCTTGCTCATTCTTTGGC	CTTCTACCCTTCTGACATTCTCTAAC
XML-Cre	CGCGGATCCACAGCCACCATGCCACAAT	CGCGGATCCACAGCCACCATGCCACAATTT

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