SUPPLEMENTAL INFORMATION

Supplemental Methods

Recombinant Plasmids, and Transfection

Full-length mouse JPH2 cDNA was amplified from pCMS-RFP-JPH2 [1] and subcloned into pcDNA3.1 (Invitrogen, Carlsbad, CA). For JPH2 RNAi transfections, 4 sets of short hairpin RNA (shRNA) oligonucleotides specific to mouse *JPH2* were cloned into pBS/U6-LoxP vector [2] (a kind gift from Dr. Chu-Xia Deng).

Generation of Transgenic Mice

JPH2 shRNA oligonucleotides (Forward: 5'-gcacttggaataacggcatattcaagagataggccgttattccaagtgccttttg-3', Reverse: 5'-aattcaaaaaggcacttggaataacggcctatctcttgaatatgccgttattccaagtgc-3') were ligated and cloned into pBS/U6-ploxPneo transgenic vector [2] (also a kind gift from Dr. Chu-Xia Deng) according to a previously described protocol [3]. Cardiac specific JPH2 overexpression (OE) mice were generated by subcloning mouse JPH2 cDNA into an αMHC transgenic vector (kindly provided by Dr. Thomas Cooper)[4]. The transgenic vectors were injected into the pronuclei of fertilized C57/BL6 oocytes, which were transferred to pseudopregnant recipients. Transgenic offspring (shJPH2) was crossed with MHC-MerCreMer (MCM) mice (Jackson laboratory, Bar Harbor, ME) [5] to generate double transgenic mice (MCM-shJPH2). MCM-shJPH2 mice were crossed with OE mice to obtain triple transgenic MCM-shJPH2-OE mice. Three to five month old male MCM, MCM-shJPH2 and MCM-shJPH2-OE mice were treated with daily 100 μl tamoxifen (Sigma-Aldrich Co., St. Louis, MO) intraperitoneal injections (~30 mg/kg) for 5 consecutive days. All mice were treated in accordance with Baylor College of Medicine Animal Care and Use Committee.

Northern Blot

Total RNA was extracted from left ventricular tissue using TRIzol reagent (Invitrogen, Carlsbad, CA). Ten μg of RNA was run in a 15% denaturing urea gel, and transferred to a Hybond N+ membrane (GE Healthcare, UK). A JPH2 probe was prepared using the *mir*Vana probe preparation kit (Ambion, Austin, TX), following the kit procedures.

RT-PCR

One μg of RNA was reverse transcribed using Superscript II and oligo(dT) primer (Invitrogen, Carlsbad, CA). RTPCR was performed in duplicate in 96-well plates using SYBR Green and a Mastercycler ep realplex (Eppendorf, Hamburg, Germany), as described [6, 7]. Expression levels were compared using the relative Ct method.

Western Blotting

Heart lysates were prepared from flash-frozen mouse hearts as described previously [8]. Heart lysate aliquots were size-fractionated on 6% (for RyR2), 7.5% (for JPH2), 12% (for Cav1.2, NCX1, SERCA2a, CaMKII, and GAPDH), or 15% (for PLN) SDS-polyacrylamide gels. Only for PLN-monomer blots, heart lysates were heated at 70°C for 10 min in 1x sample loading buffer containing 5% β-mercaptoethanol before loading on gels. The resolved gels were electro-transferred on PVDF membranes. The membranes were probed with anti-pSer2808-RyR2 (1:1,000; [8]), anti-pSer2814-RyR2 (1:500; [8]), anti-pSer16-PLN (1:5,000), or anti-pThr17-PLN (1:2,500) (both from Badrilla Ltd., Leeds, United Kingdom) phosphoepitope-specific antibody, and/or anti-Cav1.2 (1:200; Alomone Labs, Jerusalem), or anti-NCX1 (1:500; Swant, Bellinzona, Switzerland), or anti-SERCA2a (1:500; Santa Cruz Biotechnology, Santa Cruz, CA) polyclonal antibody, or an anti-JPH2 antibody raised against a synthetic peptide consisting of the amino acid

sequence 458-CRPRESPQLHERETPQPEG-475 and/or anti-RyR2 (1:5,000), or anti-PLN (1:1,000) (both Thermo Fisher Scientific (Pierce), Rockford, IL), or anti-GAPDH (1:5,000; Millipore, Temecula, CA) monoclonal antibody at 4°C overnight or at room temperature for 4 h. Blots were developed using Alexa-Fluor680-conjugated anti-mouse (Invitrogen Molecular Probes, Carlsbad, CA) and/or IR800Dye-conjugated anti-rabbit fluorescent secondary antibodies (Rockland Immunochemicals, Gilbertsville, PA), and scanned on an Odyssey infrared scanner (Li-Cor, Lincoln, NE). Integrated densities of protein bands were measured using ImageJ Data Acquisition Software (National Institute of Health, Bethesda, MD). Protein-signal densities were normalized to the corresponding GAPDH-signal densities, while phosphorylation signal densities were normalized to the corresponding total protein-signal densities, and used for plotting data.

Co-Immunoprecipitation Assay

In order to immunoprecipitate RyR2 from lysates, an anti-RyR2 antibody (Thermo Scientific, Rockland, IL) was incubated with Protein A-Sepharose beads (Rockland, Gilbertsville, PA) at RT for 1 h. Following which, this antibody attached beads were incubated with heart-lysate aliquots, containing 500 μg total protein, in a reaction volume of 300 μL at 4°C overnight. The reaction volume was made up with the homogenization buffer. At the end of the incubation, beads were washed with the homogenization buffer and then resuspended in 2x LDS buffer (Invitrogen, Carlsbad, CA) containing β-mercaptoethanol. The samples were heated at 50°C for 10 min, and were subjected to Western Blotting as described above.

Immunohistochemistry

Isolated cardiomyocytes were fixed in 2% paraformaldehyde for 10 min followed by 100 mM glycine in PBS (pH 7.4) for 10 min. Cells were washed twice for 10 min in PBS and permeabilized in PBS with 0.1% Triton X-100 for 10 min. Following two 10 min washes in PBS, the cells were incubated overnight at 4°C in antibody buffer (75 mM NaCl, 18 mM Na_3 citrate, 2% goat serum, 1%

BSA, 0.05% Triton X-100, 0.02% NaN_3, pH7.4) with mouse monoclonal RyR2 antibody (Thermo Scientific-Affinity BioReagents, Rockford, IL) and rabbit polyclonal $Ca_v1.2$ antibody (Alomone Labs, Jerusalem, Israel). The cells were washed twice for 10 min in wash buffer (75 mM NaCl, 18 mM Na_3 citrate, 0.05% Triton X-100, pH7.4) and incubated in antibody buffer with anti-mouse Alexa 568 and anti-rabbit Alexa 488 secondary antibodies (Invitrogen, Carlsbad, CA) for 2 hrs. Cells were resuspended in 50 μl mounting buffer (90% glycerol, 10% 10x PBS, 2.5% triethylenediamine, 0.02% NaN_3) and transferred to frosted slides. Isolated cardiomyocytes were resuspended in HEPES buffer at room temperature, then plated on laminin-coated dishes in 1mL of HEPES buffer and incubated at 37°C for 15 min. Cells were then washed with HEPES buffer and incubated for 1hr at RT. Imaging was performed using a laser scanning confocal microscope (LSM 510, Carl Zeiss, Thornwood, NY) with a 63X oil immersion objective. Pearson's correlation coefficient for colocalization was assessed using Zen 2008 software (Carl Zeiss, Thornwood, NY).

Histology

Hearts were fixed in 4% buffered formaldehyde, dehydrated with ethanol and histoclear, and embedded in paraffin. Tissues were sectioned longitudinally (5 μm), and stained with hematoxylin and eosin using standard protocols [9]. Cardiomyocyte cross-sectional areas were measured in sections stained with wheat germ agglutinin as described before [6].

Transthoracic Echocardiography

Mice were anesthetized using 1-2.0% isoflurane in 95%. Cardiac function was assessed using M-mode echocardiograms acquired with a VisualSonics VeVo 770 Imaging System (VisualSonics, Toronto, Canada), as described [10].

Cardiomyocyte Isolation and Ca^{2+} Imaging

Mouse ventricular myocytes were isolated as described [6]. Briefly, the heart was removed following isoflurane anesthesia and rinsed in 0 Ca^{2+} Tyrode solution (137 mM NaCl, 5.4 mM KCl, 1 mM $MgCl_2$, 5 mM HEPES, 10 mM glucose, 3 mM NaOH, pH 7.4). The heart was cannulated through the aorta and perfused on a Langendorf apparatus with 0 Ca^{2+} Tyrode (3 ~ 5 minutes, 37 °C), then 0 Ca^{2+} Tyrode containing 20 μg/ml (0.104 a.u./ml) Liberase TH Research Grade (Roche Applied Science) for 10 ~ 15 minutes at 37 °C. After digestion, the heart was perfused with 5 ml KB solution (90 mM KCl, 30 mM K_2HPO_4, 5 mM $MgSO_4$, 5 mM pyruvic acid, 5 mM β-hydroxybutyric acid, 5 mM creatine, 20 mM taurine, 10 mM glucose, 0.5 mM EGTA, 5 mM HEPES, pH 7.2) to wash out collagenase. The left ventricle of the heart was minced in KB solution and gently agitated, then filtered through 210 μm polyethylene mesh. After settling, ventricular myocytes were washed once with KB solution, and stored in KB solution at room temperature before use. Ventricular myocytes were incubated with 2 μM Fluo-4-acetoxymethyl ester (Fluo-4 AM, Invitrogen, Carlsbad, CA) in normal Tyrode solution containing 1.8 mM Ca^{2+} for 30 minutes at RT. Cells were then washed with dye-free normal Tyrode solution for 15 minutes for de-esterification and transferred to a chamber with a pair of parallel electrodes on a laser scanning confocal microscope (LSM 510, Carl Zeiss, Thornwood, NY) After being paced at 1 Hz for at least 2 minutes and steady state Ca^{2+} transients were observed, pacing was stopped for 45 seconds and spontaneous Ca^{2+} release events and Ca^{2+} sparks were counted. Steady state SR Ca^{2+} content was estimated by rapid application of 10 mM caffeine after pacing.

T-Tubule Imaging and Analysis.

T-Tubules of ventricular myocytes was visualized by Di-8-ANEPPS staining (10 μM for 10 min) in normal Tyrode solution with 1.8 mM Ca^{2+}. Quantitative analysis of spatial integrity of T-Tubules was modified from previous studies [11, 12] and was performed with ImageJ software (http://rsb.info.nih.gov/ij/). Region of interest was selected within a cell and outside of nucleus.

Power spectrum was computed using Fast Fourier Transform (FFT). Normalized power at spatial frequency of ~0.55 μm^{-1} (peak power at ~0.55 μm^{-1} normalized to average power at spatial frequency of 0.2 to 0.4 μm^{-1}) was used as an index of the spatial integrity of T-Tubules (TT-Power).

Electrophysiology

Membrane currents were measured using whole cell patch clamp techniques with an Axopatch 200B amplifier, DigiData 1440a digitizer and pCLAMP v.10 software (Molecular Devices, Sunnyvale, CA). Ventricular myocytes were perfused with normal Tyrode solution with 1.8 mM Ca^{2+}. Pipette resistances were 1.5 - 3 mΩ prior to sealing. Electrode solution contained 110 mM CsCl, 20 mM tetraethylammonium chloride, 10 mM glucose, 10 mm HEPES, and 5 mM Mg-ATP (pH 7.2 adjusted with CsOH). Cells were voltage clamped at -80 mV in whole cell configuration. Prior to recording the holding potential was changed from -80 mV to -40 mV to inactivate Na^+ current (I_{Na}). I-V curves were generated using 500 ms depolarizing voltage steps from -40 to +40 mV in 10 mV increments. All currents were normalized to cell capacitances before comparison.

Excitation-Contraction Coupling Gain

To investigate EC coupling gain, confocal Ca^{2+} imaging and whole cell patch clamp techniques were employed simultaneously [13]. Ten pre-pulses at 0.2 Hz were applied to equalize SR Ca^{2+} and the testing pulse was delivered 30 seconds later. The EC coupling gain is expressed as the ratio of the amplitude of Ca^{2+} transient (ΔF/F0) and the amplitude of $I_{Ca,L}$ (pA/pF). Data was analyzed offline using Clampfit (Axon Instruments, CA) and Zen 2008 (Carl Zeiss, Thornwood, NY).

Electron Microscopy

Small sections of left ventricular apex were fixed in 0.1 M sodium cacodylate buffer (pH 7.2) containing 2.5% glutaraldehyde, post-fixed in 1% tannic acid and transferred to 1% osmium tetroxide. Specimens were dehydrated through an acetone series and embedded in resin. Thin plastic sections (80 to 100 nm) were cut, stained with uranyl acetate and lead citrate, and imaged on a Tecnai G^2 Spirit BioTWIN (FEI Company, Hillsboro, OR) electron microscope.

Co-immunoprecipitation

Anti-RyR2 antibody (Thermo Scientific, Rockland, IL) was incubated with Protein A-Sepharose beads (Rockland, Gilbertsville, PA) at RT for 1 h and incubated with heart lysates containing 500 μg total protein. Beads were washed and resuspended in 2x LDS buffer (Invitrogen, Carlsbad, CA) containing β-mercaptoethanol. The samples were heated at 50°C for 10 min, and were resolved on SDS-PAGE gels.

Computational Model

The modifications of the Luo-Rudy myocyte simulation model [14] will be described in detail elsewhere. The discrete Ca^{2+} release myocyte model was paced to a steady state at a basic cycle length (BCL) of 1000 ms. The myocyte was then held at a membrane potential of -88 mV for 100 ms before being clamped at 0 mV for a duration of 100 ms. The depth of the dyad is defined as the distance between the voltage-gated Ca^{2+} channels (VGCC) and type 2 ryanodine receptors (RyR2).

Statistical Analysis

Data are expressed as mean ± SEM. Statistical significance of differences between experimental groups was compared using Student's *t*-test, one-way ANOVA with pairwise multiple comparisons performed using the Student-Newman-Keuls method as appropriate. If results failed a normality

test, the Wilcoxon rank sum or Kruskal-Wallis tests were used, as appropriate. A value of $P<0.05$ was considered statistically significant.

Supplemental References

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Supplemental Figure Legends.

Legend Supplemental Figure 1. Inducible cardiac-specific JPH2 knockdown mice causes mortality and acute heart failure

a. Schematic representation of vectors used to express JPH2 and different shRNAs targeting JPH2 in HEK cells. **b.** Western blot analysis of HEK cell lysates after co-transfection with JPH2 and 4 different shRNAs or empty vector (e.v.), respectively. Mouse heart lysate (H) was used as positive control for JPH2 detection. **c.** Quantitative PCR analysis of OAS1 and STAT1 mRNA levels in cardiac tissue from MCM (n=7) and MCM-shJPH2 (n=7) mice, indicating the absence of interferon response activation. **d.** Left ventricular posterior wall thickness in diastole (LVPWd) of MCM (17) and MCM-shJPH2 (14) mice at 1 week after completion of tamoxifen administration. **e**. Bar graph showing normalized cardiomyocyte area calculated from wheat germ agglutinin (WGA) stained sections. Numbers indicate number of cells (number of mice). **f**. Bar graph showing increased lung weight to tibia length in MCM-shJPH2 mice compared to MCM. Numbers in bar indicate number of mice. **g.** Quantitative PCR analysis of cardiac stress markers Acta1, ANF, BNP, βMHC, and RCAN1-4 in hearts from MCM and MCM-shJPH2 mice (n=7 each group). Data are represented as mean ± SEM; * $P<0.05$ versus MCM control.

Legend Supplement Figure 2. Altered morphology of T-Tubules following knockdown of JPH2.

a-b. Bright field **(a)** and confocal fluorescence images **(b)** of representative di-8-ANEPPS-stained single ventricular myocytes isolated from tamoxifen-treated MCM (left) and MCM-shJPH2 (right) mice. **c.** Respective high resolution views and binary imaged (threshold at mean pixel intensity) of areas within the red rectangles in panel b. **e.** Corresponding Fast Fourier transformed images of T-

Tubule images shown in panel c. **f.** Representative power vs. spatial frequency along the x axis computed using Fourier analysis. **g.** Bar graph showing normalized power at spatial frequency of ~0.55 μm^{-1} (as indicated by the arrow in panel e). Scale bar = 10 μm. *** $P<0.001$ versus MCM control. n = 21 cells from 5 tamoxifen-treated MCM and 6 MCM-shJPH2 mice.

Legend Supplemental Figure 3. Inducible cardiac-specific JPH2 knockdown does not alter expression and phosphorylation levels of other calcium-handling proteins.

a. Representative Western blots of cardiac tissue lysates from MCM (n=6) and MCM-shJPH2 (n=6) mice showing expression levels of Na^+/Ca^{2+}-exchanger (NCX1), sarcoplasmic reticulum Ca^{2+} ATPase 2 (SERCA2) and calsequestrin 2 (Casq2). **b.** Bar graphs summarizing quantitative analyses of the Western Blots shown in **a**. Protein expression levels were normalized first to corresponding GAPDH levels and then to average MCM value. **c, e.** Representative Western blot analyses of cardiac tissue lysates from MCM (n=6) and MCM-shJPH2 (n=6) mice showing expression and phosphorylation levels of ryanodine receptor 2 (RyR2; panel **c**) and phospholamban (PLN; panel **e**) at protein kinase A site (pS2808) and calcium calmodulin kinase II site (pS2814). **d, f.** Bar graphs summarizing quantitative analyses of the Western Blots shown in **c** and **e** respectively. RyR2 and PLN phosphorylation levels were normalized first to respective total protein expression levels and then to average MCM value. Data are represented as mean ± SEM.

Legend Supplemental Figure 4. Inducible cardiac-specific JPH2 knockdown decreases expression level of JPH2 and its interaction with RyR2 to similar extents.

a. Representative Western blots of cardiac tissue lysates and immunoprecipitates (IP) from MCM (n=4) and MCM-shJPH2 (n=5) mice showing expression levels of ryanodine receptor 2 (RyR2) and junctophilin 2 (JPH2). RyR2 was immunoprecipitated using anti-RyR2 antibody from cardiac lysates (right). **b.** Bar graphs summarizing quantitative analyses of the Western Blots shown in **a**.

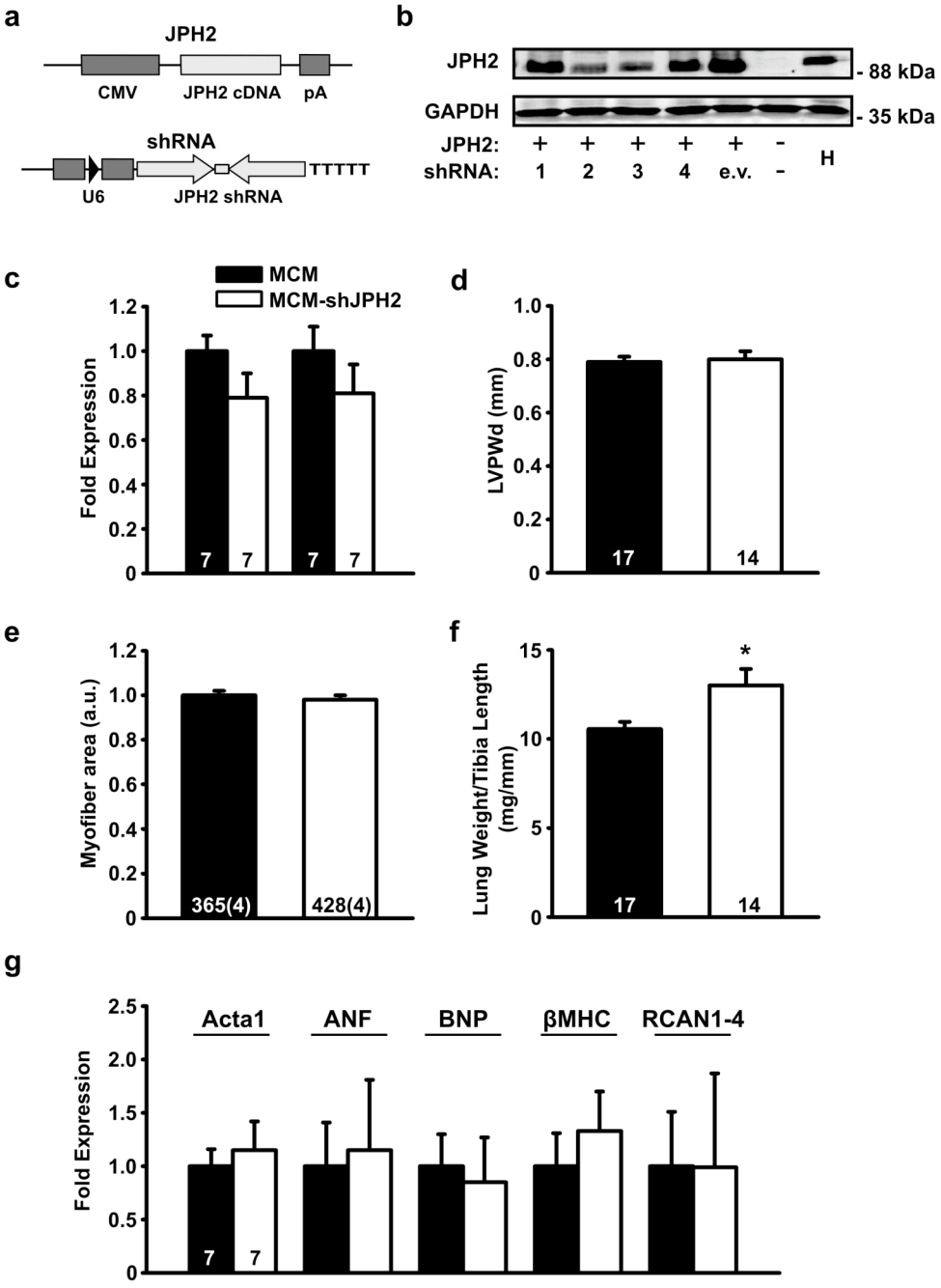
Protein expression levels were normalized to average MCM value. Data are represented as mean ± SEM; * $P<0.05$ and ** $P<0.005$, both versus MCM control.

Supplemental Table. Left ventricular echocardiographic parameters of MCM, MCM-shJPH2 line 21, MCM-shJPH2 line 38 and MCM-shJPH2 line38-OE mice at one week after finalizing tamoxifen treatment.

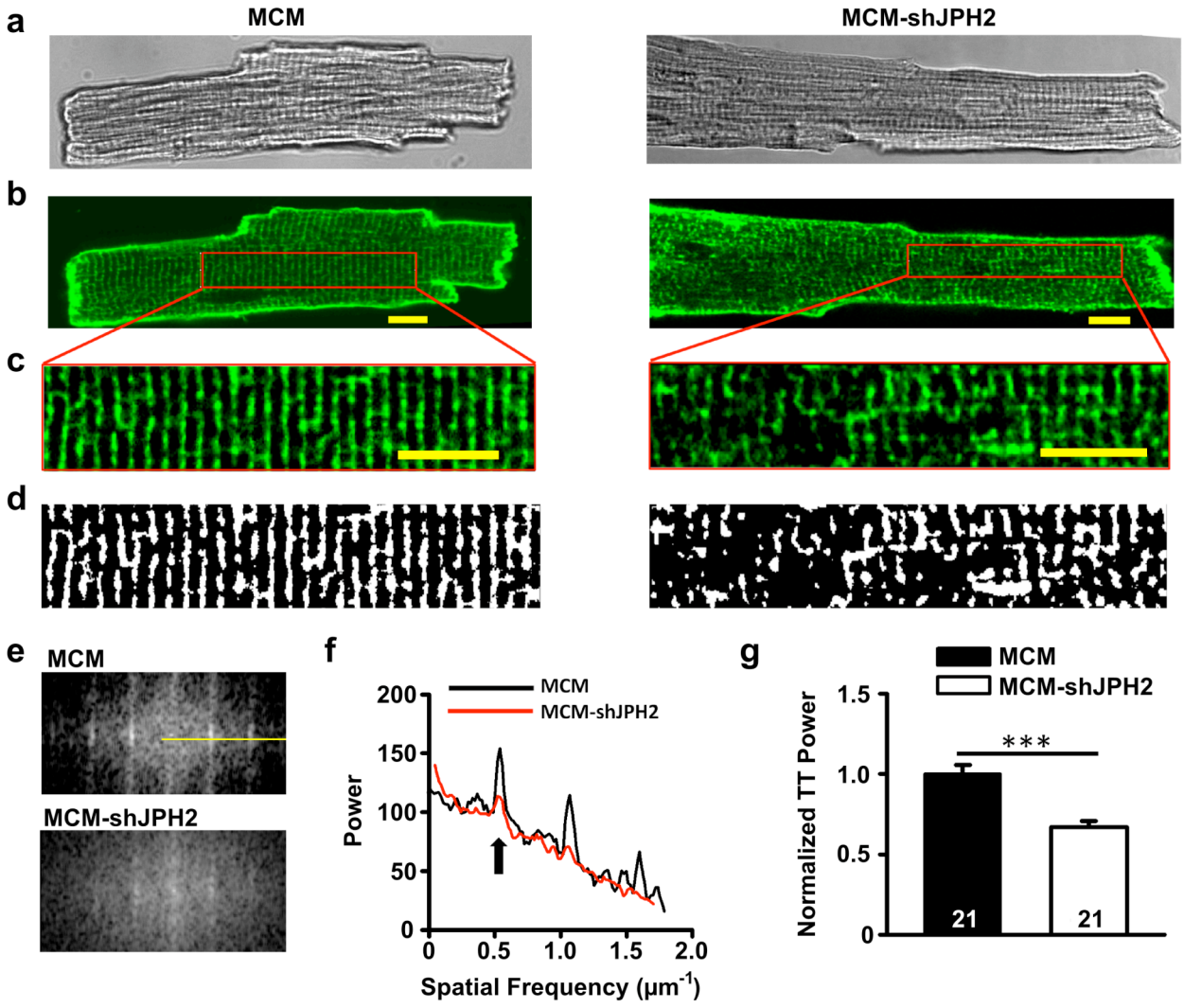
	MCM	MCM-shJPH2 line 21	MCM-shJPH2 line 38	MCM-shJPH2-OE
	(n=17)	(n=11)	(n=14)	(n=8)
BW (g)	37.0 ± 0.8	35.2 ± 1.0	37.5 ± 1.7	35.0 ± 2.1
HR (b.p.m.)	450 ± 7$^{\#}$	468 ± 10$^{**,\#}$	485 ± 11$^{*,\#\#\#}$	420 ± 4***
ESD (mm)	3.19 ± 0.07	4.11 ± 0.13$^{***,\#\#\#}$	3.89 ± 0.16$^{***,\#\#}$	3.16 ± 0.20
EDD (mm)	4.35 ± 0.06	4.80 ± 0.07$^{**,\#}$	4.73 ± 0.08$^{**,\#}$	4.37 ± 0.18
EF (%)	52.0 ± 2.2	30.3 ± 3.7$^{***,\#\#\#}$	36.7 ± 4.3$^{**,\#\#}$	54.2 ± 3.0
FS (%)	26.7 ± 1.3	14.5 ± 1.9$^{***,\#\#}$	18.2 ± 2.3$^{**,\#\#}$	28.1 ± 1.8
IVSs (mm)	0.86 ± 0.01	0.76 ± 0.02$^{***,\#}$	0.82 ± 0.02	0.83 ± 0.01
IVSd (mm)	0.76 ± 0.01	0.71 ± 0.02	0.76 ± 0.02	0.74 ± 0.01
LVPWs (mm)	1.13 ± 0.02	1.02 ± 0.06	1.03 ± 0.05	1.02 ± 0.03
LVPWd (mm)	0.79 ± 0.02	0.83 ± 0.04	0.80 ± 0.03	0.72 ± 0.03

BW = body weight; HR = heart rate; b.p.m. = beats per minutes; ESD = end-systolic diameter; EDD = end-diastolic diameter; EF = ejection fraction; FS = left ventricular fractional shortening; IVS = intraventricular septal wall thickness (s, systole d, diastole); LVPW = left ventricular posterior wall thickness (s, systole d, diastole). Data are expressed as mean ± SEM. * P<0.05, ** P<0.01, *** P<0.001 versus MCM. $^{\#}$ P<0.05, $^{\#\#}$ P<0.01, $^{\#\#\#}$ P<0.001 versus MCM-shJPH2-OE.

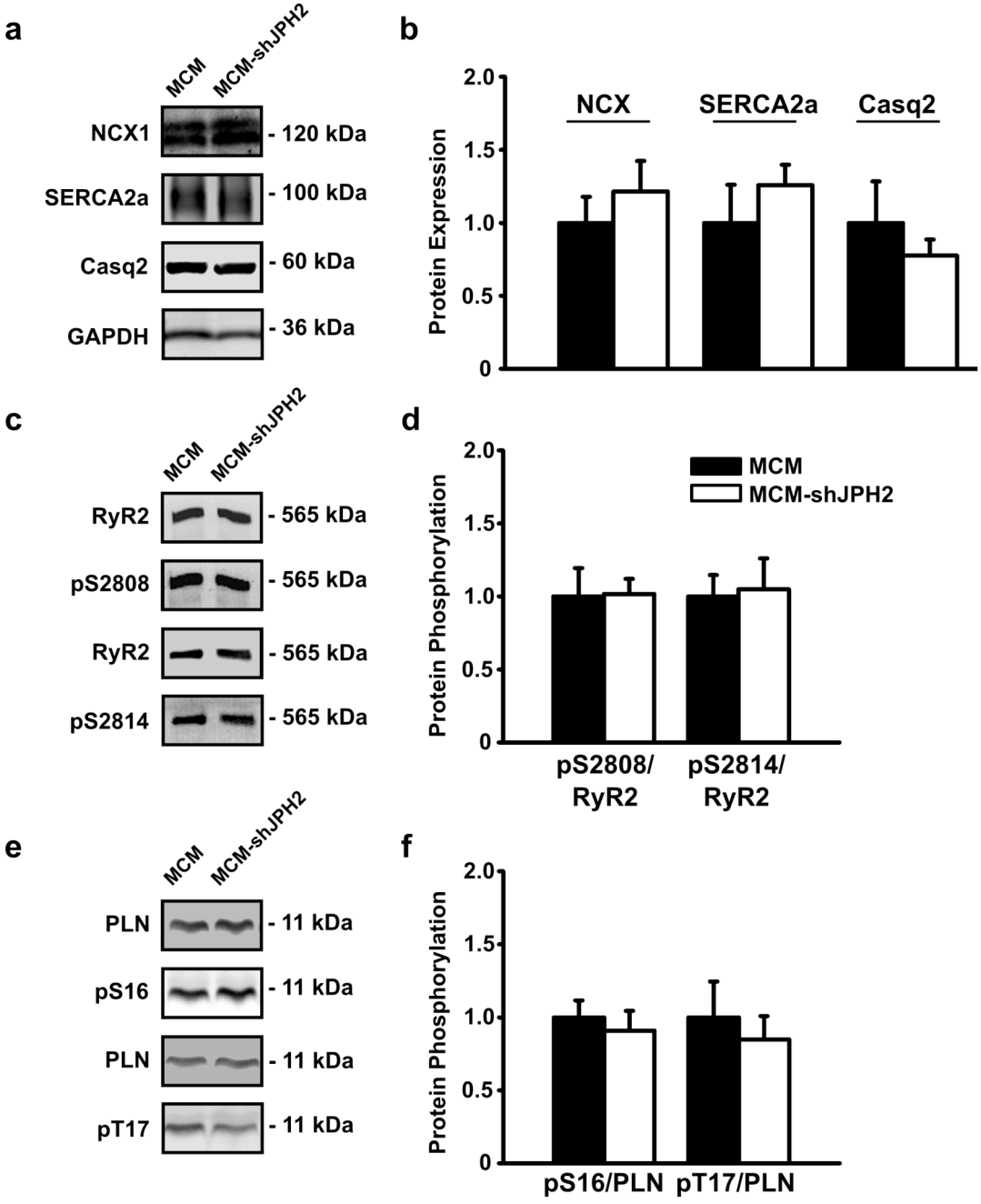
Supplemental Figure 1.



Supplemental Figure 2.



Supplemental Figure 3



Supplemental Figure 4.