ONLINE DATA SUPPLEMENT

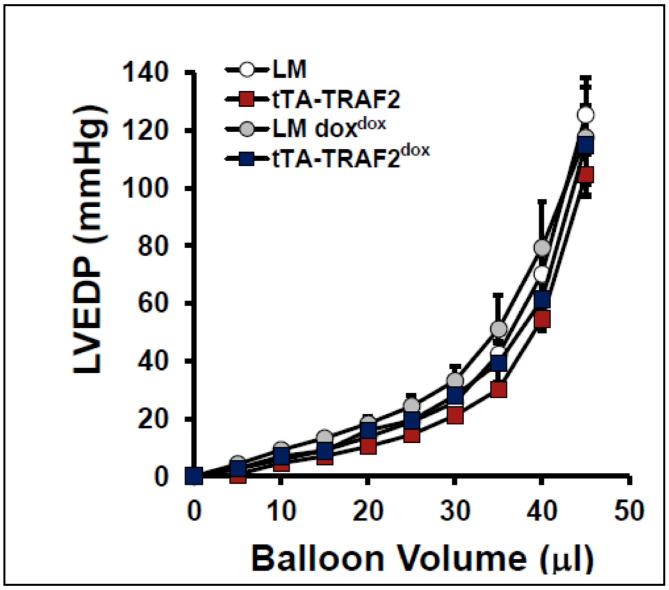

Figure S1. LV pressure volume curves in Langendorff buffer perfused LM, tTA-TRAF2, LM^{dox}, and tTA-TRAF2^{dox4W} hearts. After 20 minutes of stabilization, the LV balloon was progressively inflated in 5 µl increments and LV end-diastolic pressure (LVEDP) measured after each balloon inflation (n = 4 hearts/group).

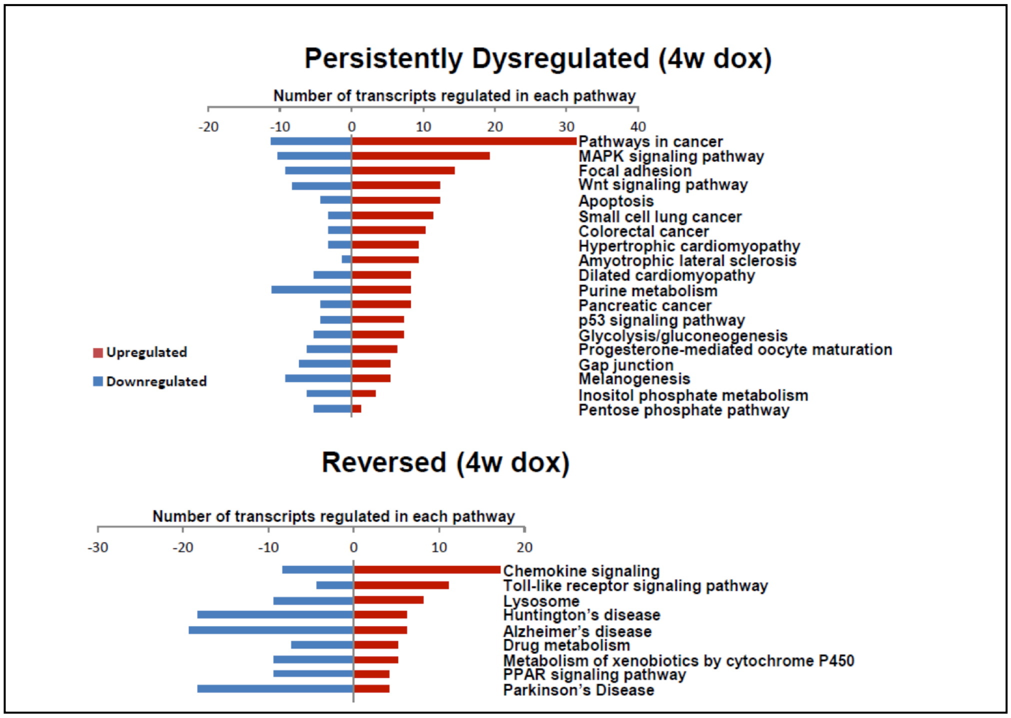

Figure S2. Gene Ontology analysis of functional pathways that of persistently dysregulated incident heart failure genes and reversed incident heart failure genes in the tTA-TRAF2^{dox4w} mouse hearts following 4 weeks of treatment with doxycycline.

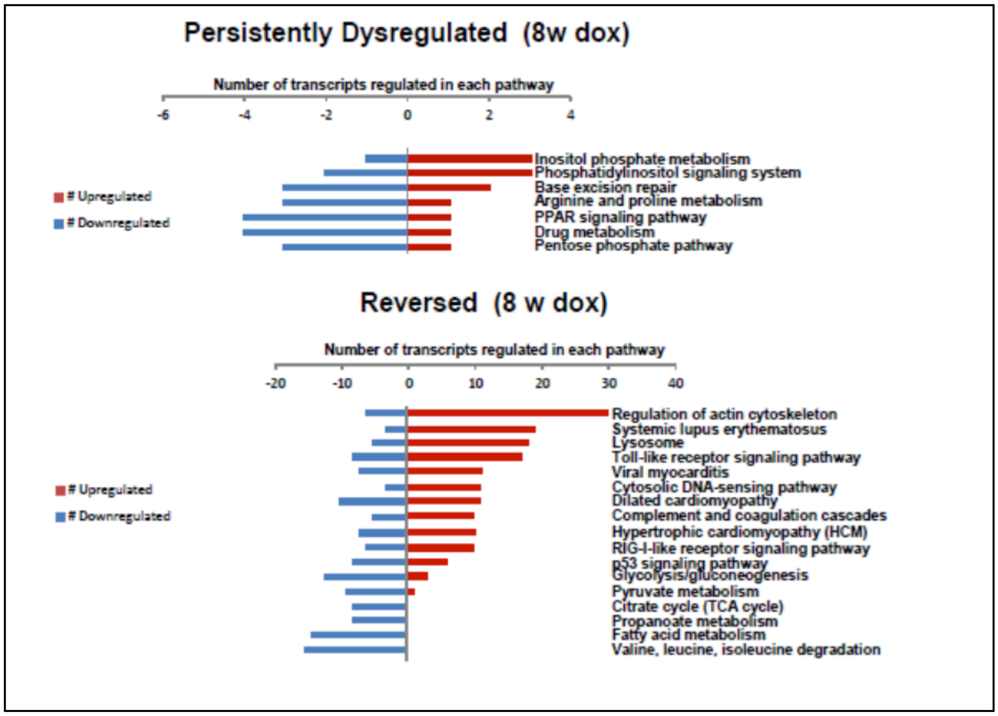

Figure S3. Gene Ontology analysis of functional pathways that were in the family of persistently dysregulated incident heart failure genes and the reversed heart failure genes in the tTA-TRAF2^{dox8w} mouse hearts following 8 weeks of treatment with doxycycline.

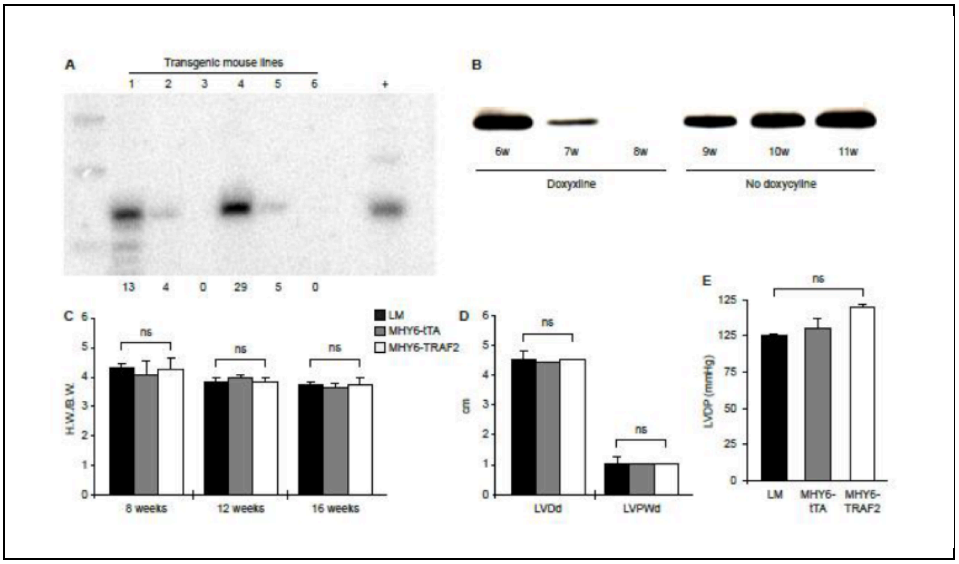

Figure S4. Generation and characterization of tTA-TRAF2 mice. (A) Representative southern blot showing four lines of mice expressing 4, 5, 13 and 29 copies of the TRAF2 transgene (B) Western blot of TRAF2 protein expression in heart of a tTA-TRAF2 mouse heart after administering doxycycline from 6 - 8 weeks of age, and after stopping doxycycline from 8 – 11 weeks of age. (C) HW/BW ratio of littermate (LM), MHY6-tTA and MHY6-TRAF2 mice at 8, 12 and 16 weeks of age. (D) Left ventricular end-diastolic dimension (LVDd) and left ventricular posterior wall thickness (LVPWd) in 12 week LM, MHY6-tTA and MHY6-TRAF2 mouse hearts; (E) left ventricular developed pressure (LVDP) in in 12 week LM, MHY6-tTA and MHY6-TRAF2 mouse hearts.

Supplemental Table I: Gene Ontology Analysis of Functional Pathways of New Reverse Remodeled Genes in the tTA-TRAF2$^{\mathrm{dox4W}}$ mice

KEGG Pathway	p-value	Number of genes upregulated	Number of genes downregulated
Ubiquitin mediated proteolysis	$1.4\mathrm{x}10^{-2}$	9	11
SNARE interactions in vesicular transport	$3.2\mathrm{x}10^{-2}$	6	2
JAK-STAT signaling pathway	$4.1\mathrm{x}10^{-2}$	8	12
Cytokine-cytokine receptor interaction	$4.1\mathrm{x}10^{-2}$	10	19
RIG-I-like receptor signaling pathway	$4.9\mathrm{x}10^{-2}$	3	8
Cardiac muscle contraction	$5.2\mathrm{x}10^{-2}$	4	7
Regulation of autophagy	$5.5\mathrm{x}10^{-2}$	0	7
Arrhythmogenic right ventricular cardiomyopathy (ARVC)	$8.4\mathrm{x}10^{-2}$	6	5
Proteasome	$8.6\mathrm{x}10^{-2}$	6	2

Supplemental Table II: Changes in Gene Expression in tTA-TRAF2^{dox4W} Mice

Symbol	Gene Name	Expression level (relative to LM)	p value
		Reversed Incident HF	
Timp3	TIMP metallopeptidase inhibitor 3	1.78	7.61x10^{-5}
Sgcd	sarcoglycan, delta (35kDa dystrophin-associated glycoprotein)	1.51	1.17x10^{-2}
Col1a1	collagen, type I, alpha 1	1.35	3.79x10^{-2}
Tpm3	tropomyosin 3	1.32	3.25x10^{-2}
Dag1	dystroglycan 1 (dystrophin-associated glycoprotein 1)	-1.21	3.52x10^{-2}
Itga6	integrin, alpha 6	-1.21	4.66x10^{-2}
Mmp11	matrix metallopeptidase 11 (stromelysin 3)	-1.24	5.30x10^{-3}
Mmp15	matrix metallopeptidase 15 (membrane-inserted)	-1.26	4.89x10^{-2}
Tgfbr3	transforming growth factor, beta receptor III	-1.27	1.82x10^{-2}
Mmp21	matrix metallopeptidase 21	-1.28	2.63x10^{-2}
Mmp8	matrix metallopeptidase 8 (neutrophil collagenase)	-1.32	3.25x10^{-2}
Igf1	insulin-like growth factor 1 (somatomedin C)	-1.32	3.16x10^{-2}
Adcy6	adenylate cyclase 6	-1.53	2.75x10^{-3}
Cacng3	calcium channel, voltage-dependent, gamma subunit 3	-1.54	1.77x10^{-2}
		Persistently Dysregulated	
Myh7	myosin, heavy chain 7, cardiac muscle, beta	6.73	3.12x10^{-7}
Tgfb3	transforming growth factor, beta 3	3.88	5.09x10^{-9}
Tgfb2	transforming growth factor, beta 2	2.76	1.60x10^{-8}
Mmp23	matrix metallopeptidase 23	2.58	2.52x10^{-7}
Cacnb1	calcium channel, voltage-dependent, beta 1 subunit	2.56	2.79x10^{-9}
Des	desmin	1.96	9.04x10^{-4}
Prkab2	protein kinase, AMP-activated, beta 2 non-catalytic subunit	1.83	1.09x10^{-3}
Itga9	integrin, alpha 9	1.72	2.45x10^{-4}
Prkaca	protein kinase, cAMP-dependent, catalytic, alpha	1.50	5.85x10^{-3}
Timp2	TIMP metallopeptidase inhibitor 2	1.49	5.00x10^{-5}
Ace	angiotensin I converting enzyme (peptidyl-dipeptidase A) 1	1.40	3.77x10^{-2}
Lmna	lamin A/C	1.34	2.57x10^{-2}
Itgb4	integrin, beta 4	-1.25	1.05x10^{-2}
Tpm2	Tropomyosin 2 (Beta)	-1.40	2.58x10^{-2}
Prkx	protein kinase, X-linked	-1.42	3.41x10^{-2}
Itgb6	integrin, beta 6	-1.45	6.08x10^{-2}
Mmp17	matrix metallopeptidase 17 (membrane-inserted)	-1.45	4.70x10^{-3}
Adcy8	adenylate cyclase 8	-1.54	1.54x10^{-4}

Changes in gene expression in tTA-TRAF2^{dox4W} mice vs. LM control mice at 12 weeks of age identified by the KEGG functional pathway for cardiac hypertrophy/dilated cardiomyopathy were modified to include changes in extracellular matrix gene expression that have been linked to the development of dilated cardiomyopathy. Changes in gene expression are displayed visually in Figure 4 D-E in the manuscript.

Supplemental Table III: Gene Ontology Analysis of Functional Pathways of New Reverse Remodeled Genes in tTA-TRAF2^{dox8W} mice

KEGG Pathway	p-value	Number of genes upregulated	Number of genes downregulated
JAK-STAT signaling pathway	2.2×10^{-2}	6	8
Complement and coagulation cascade	5.6×10^{-2}	3	5
Androgen and estrogen metabolism	6.3×10^{-2}	3	2
Pathways in cancer	6.7×10^{-2}	13	8

Supplemental Table IV: Changes in Gene Expression in tTA-TRAF2^{dox8W} Mice

Symbol	Gene Name	Expression level (relative to LM)	p value
		Reversed Incident HF	
Myh7	myosin, heavy chain 7, cardiac muscle, beta	7.99	2.85x10^{-5}
Tgfb3	transforming growth factor, beta 3	4.18	1.07x10^{-5}
Cacnb1	calcium channel, voltage-dependent, beta 1 subunit	2.94	1.83x10^{-4}
Tgfb2	transforming growth factor, beta 2	2.94	4.77x10^{-6}
Timp1	TIMP metallopeptidase inhibitor 1	2.68	3.04x10^{-2}
Mmp23	matrix metallopeptidase 23	2.44	3.20x10^{-5}
Adcy1	adenylate cyclase 1 (brain)	1.59	1.31x10^{-2}
Des	desmin	1.57	3.66x10^{-6}
Itgb5	integrin, beta 5	1.51	2.89x10^{-4}
Itga9	integrin, alpha 9	1.49	1.62x10^{-3}
Timp3	TIMP metallopeptidase inhibitor 3	1.44	1.11x10^{-2}
Cacng6	calcium channel, voltage-dependent, gamma subunit 6	1.42	4.34x10^{-2}
Mmp2	matrix metallopeptidase 2 (gelatinase A, 72kDa gelatinase, 72kDa type IV collagenase)	1.29	2.08x10^{-2}
Tpm3	tropomyosin 3	1.29	4.54x10^{-2}
Lmna	lamin A/C	1.21	9.05x10^{-3}
Ttn	titin	-1.23	4.24x10^{-3}
Sgca	sarcoglycan, alpha (50kDa dystrophin-associated glycoprotein)	-1.23	2.61x10^{-2}
Adcy9	adenylate cyclase 9	-1.30	2.88x10^{-2}
Mmp27	matrix metallopeptidase 27	-1.32	4.49x10^{-2}
Prkaa2	protein kinase, AMP-activated, alpha 2 catalytic subunit	-1.32	1.56x10^{-2}
Tgfb1	transforming growth factor, beta 1	-1.32	4.88x10^{-2}
Prkx	protein kinase, X-linked	-1.40	4.35x10^{-2}
Myh6	myosin, heavy chain 6, cardiac muscle, alpha	-1.49	2.87x10^{-3}
Adcy8	adenylate cyclase 8	-1.54	2.85x10^{-2}
Adrb1	adrenoceptor beta 1	-1.55	5.33x10^{-3}
Cacna2d1	calcium channel, voltage-dependent, alpha 2/delta subunit 1	-1.55	2.26x10^{-3}
Itgb6	integrin, beta 6	-1.81	6.56x10^{-5}
		Persistently Dysregulated	3.41x10^{-2}
Prkab2	protein kinase, AMP-activated, beta 2 non-catalytic subunit	1.35	1.32x10^{-2}
Mmp15	matrix metallopeptidase 15 (membrane-inserted)	-1.58	3.33x10^{-4}
Cacng4	calcium channel, voltage-dependent, gamma subunit 4	-1.79	2.03x10^{-4}

Changes in gene expression in tTA-TRAF2^{dox8W} mice vs. LM control mice at 16 weeks of age identified by the KEGG functional pathway for cardiac hypertrophy/dilated cardiomyopathy were modified to include changes in extracellular matrix gene expression that have been linked to the development of dilated cardiomyopathy. Changes in gene expressed are displayed visually in Figure 6D-6E in the manuscript

Supplemental Table V: Gene Ontology Analysis of Functional Pathways of New Reverse Remodeled Genes in Human Dilated Cardiomyopathy

KEGG Pathway	p-value	Number of genes upregulated	Number of genes downregulated
Spliceosome	3.3×10^{-16}	48	0
Focal adhesion	1.7×10^{-7}	46	1
Shigellosis	2.6×10^{-6}	21	0
Adherent junction	3.5×10^{-4}	20	0
Bacterial invasion of epithelial cells	8.5×10^{-4}	20	0
Pathways in cancer	1.5×10^{-3}	61	0
ErbB signaling pathway	2.5×10^{-3}	20	1
Proteoglycans in cancer	2.7×10^{-3}	36	1
Prostate cancer	3.0×10^{-3}	21	0
RNA transport	3.8×10^{-3}	32	0
Neurotrophin signaling pathway	5.0×10^{-3}	24	1
Insulin signaling pathway	5.7×10^{-3}	26	2
Choline metabolism in cancer	6.1×10^{-3}	22	0
Chronic myeloid leukemia	6.2×10^{-3}	18	0
Regulation of actin cytoskeleton	7.1×10^{-3}	36	1
mRNA surveillance pathway	9.7×10^{-3}	20	0
FoxO signaling pathway	1.1×10^{-2}	26	0
Endometrial cancer	1.6×10^{-2}	14	0
Notch signaling pathway	2.1×10^{-2}	13	0
Small cell lung cancer	2.2×10^{-2}	19	0
Acute myeloid leukemia	4.4×10^{-2}	14	0