SUPPLEMENTAL MATERIAL

Table S1. The oligonucleotide/primer sequences in this study.

Name	Sequence (5'→3')	Application
CYP2E1-ov forward	CCAAGTTGGCAAAGCGCT	Genotyping for
CYP2E1-ov reverse	AAAAGACCAAAGGCCAGCC	Cyp2e1-ov mice
CYP2E1-kd forward	GGCATGGACGAGCTGTACAA	Genotyping for
CYP2E1-kd reverse	CTCTAGATCAACCACTTTGT	Cyp2e1-kd mice
CYP2E1-ChIP forward	CCTGGATGAACAAGCACA	ChIP
CYP2E1-ChIP reverse	GGCAAGAGCACCTGAAAG	PCR primer
pGL3-cyp2e1(-350~+37) forward	GGAATGGTACCCCAGTGCCATGGGGAAGAC	PCR primer
pGL3-cyp2e1(-350~+37) reverse	TTCTCGAGAGACAAGCAAGGCAACGGT	PCR primer
pGL3-cyp2e1(-700~+37) forward	GGAATGGTACCTGCCTAGCATGTGCAAGGC	PCR primer
pGL3-cyp2e1(-700~+37) reverse	TTCTCGAGAGACAAGCAAGGCAACGGT	PCR primer
pGL3-cyp2e1(-855~+37) forward	GGAATGGTACCCTGGATGAACAAGCACATG	PCR primer
pGL3-cyp2e1(-855~+37) reverse	TTCTCGAGAGACAAGCAAGGCAACGGT	PCR primer
pGL3-cyp2e1(-1508~+37) forward	GGAATGGTACCTCCTGCTCTCGGGACCTTT	PCR primer
pGL3-cyp2e1(-1508~+37) reverse	TTCTCGAGAGACAAGCAAGGCAACGGT	PCR primer

ChIP, chromatin immunoprecipitation assay.

Table S2. The sequencing results of the mutated vectors in this study.

Name	Sequence (5'→3')
pGL3-0.9cyp2e1(CEBP and MYC mut)	>cyp2e1(-850~+36,delete -846~-835 and -756~-743) ggtaccCTGGATGAAACAAATCCAATTTTTAAAAAATTTCTTCTTTTTTTCTTCTGTATTTGACAA AGTGTTTTGAAAAACATTTTCCACCTAAGTGGGGCTGTTGAAGGAC AGGTAGTACCTTTCAGGTGCTCTTGCCTAGCATGTGCAAGGCCCTGGGTTTGGTCCTTGG CACTGCAAATATTCGCTTACACAGACACTCAGAATATCTCAAAGTGCTTTAGCTTTATTT ACCTCTACTTTTTTGCCTCCATGGAATTTTCTGGTTGATTTGACAACGTGAAATGGGATC CAGAAGTGAGATTTCCTGTTCTGCCCTCAATTTCCAGGTGGGCCATTAGGGTTGTGGTGC CAGATCAGAAGTTAGAGGTCTGCAGCCTAGTGCTGTCTTTGGCCTGGAATGAGCAGTAAA TGGTTGGAAAAAAAACCTTTCCCAGCAAACAAACACATGCAAACATGATCTGAATGCATG CCTTCTGTGCTGACCAGTGCCATGGGGAAGACATTCCCCCACCCCCAGGACTGACCTATG AATTGGTGAGGTATTCCTACATGTACTCACCAGCACCCTGACAGGTGCCAGCAACCAGAG GATTGGCAGGGCCCAGCCTCATCCTTGTCAGATCAGTAGATGCAACTTCTAAGAGGCAAT GGCTCCAAGGGTCAGCCTTTGAAATGATAGCCAACTGCAGCTAATAATAAACCAGCACTT TAGGCCAAGGGAGATGAGTGGTTATTGGCTGATGAGCCACCCTCCTTCTCAACGACACGT TATAAAATCCTTGTTTCTCCTCAGGAAATTCCTACAAATTTAGAGTGGAGCCCCATCGGC ACCATGGCGGTTCTTGGCATCACCGTTGCCTTGCTTGTCTCTCGAG
pGL3-0.9cyp2e1(CEBP mut)	>cyp2e1(-850~+36,delete -846~-835) ggtaccCTGGATGAAACAAATCCAATTTTTAAAAAATTTCTTCTTTTTTTCTTCTGTATTTGACAA AGTGTTTTGAAAAACATTTTCCACCTACATTTTTACAAATAAGTGGGGCTGTTGAAGGAC AGGTAGTACCTTTCAGGTGCTCTTGCCTAGCATGTGCAAGGCCCTGGGTTTGGTCCTTGG CACTGCAAATATTCGCTTACACAGACACTCAGAATATCTCAAAGTGCTTTAGCTTTATTT ACCTCTACTTTTTTGCCTCCATGGAATTTTCTGGTTGATTTGACAACGTGAAATGGGATC CAGAAGTGAGATTTCCTGTTCTGCCCTCAATTTCCAGGTGGGCCATTAGGGTTGTGGTGC CAGATCAGAAGTTAGAGGTCTGCAGCCTAGTGCTGTCTTTGGCCTGGAATGAGCAGTAAA TGGTTGGAAAAAAAACCTTTCCCAGCAAACAAACACATGCAAACATGATCTGAATGCATG CCTTCTGTGCTGACCAGTGCCATGGGGAAGACATTCCCCCACCCCCAGGACTGACCTATG AATTGGTGAGGTATTCCTACATGTACTCACCAGCACCCTGACAGGTGCCAGCAACCAGAG GATTGGCAGGGCCCAGCCTCATCCTTGTCAGATCAGTAGATGCAACTTCTAAGAGGCAAT GGCTCCAAGGGTCAGCCTTTGAAATGATAGCCAACTGCAGCTAATAATAAACCAGCACTT TAGGCCAAGGGAGATGAGTGGTTATTGGCTGATGAGCCACCCTCCTTCTCAACGACACGT TATAAAATCCTTGTTTCTCCTCAGGAAATTCCTACAAATTTAGAGTGGAGCCCCATCGGC ACCATGGCGGTTCTTGGCATCACCGTTGCCTTGCTTGTCTCTCGAG
pGL3-0.9cyp2e1(MYC mut)	>cyp2e1(-850~+36,delete -756~-743) ggtaccCTGGATGAACAAGCACATGGAACAAATCCAATTTTTAAAAAATTTCTTCTTTTTTTCTTC TGTATTTGACAAAGTGTTTTGAAAAACATTTTCCACCTAAGTGGGGCTGTTGAAGGACAG GTAGTACCTTTCAGGTGCTCTTGCCTAGCATGTGCAAGGCCCTGGGTTTGGTCCTTGGCA CTGCAAATATTCGCTTACACAGACACTCAGAATATCTCAAAGTGCTTTAGCTTTATTTAC CTCTACTTTTTTGCCTCCATGGAATTTTCTGGTTGATTTGACAACGTGAAATGGGATCCA GAAGTGAGATTTCCTGTTCTGCCCTCAATTTCCAGGTGGGCCATTAGGGTTGTGGTGCCA GATCAGAAGTTAGAGGTCTGCAGCCTAGTGCTGTCTTTGGCCTGGAATGAGCAGTAAATG GTTGGAAAAAAAACCTTTCCCAGCAAACAAACACATGCAAACATGATCTGAATGCATGCC TTCTGTGCTGACCAGTGCCATGGGGAAGACATTCCCCCACCCCCAGGACTGACCTATGAA

TTGGTGAGGTATTCCTACATGTACTCACCAGCACCCTGACAGGTGCCAGCAACCAGAGGA
TTGGCAGGGCCCAGCCTCATCCTTGTCAGATCAGTAGATGCAACTTCTAAGAGGCAATGG
CTCCAAGGGTCAGCCTTTGAAATGATAGCCAACTGCAGCTAATAATAAACCAGCACTTTA
GGCCAAGGGAGATGAGTGGTTATTGGCTGATGAGCCACCCTCCTTCTCAACGACACGTTA
TAAAATCCTTGTTTCTCCTCAGGAAATTCCTACAAATTTAGAGTGGAGCCCCATCGGCAC
CATGGCGGTTCTTGGCATCACCGTTGCCTTGCTTGTCTCTCGAG

Table S3. Upstream regulators of CYP2E1 screened by Co-IP-MS.

Upstream Regulator	Molecule Type	p-value of overlap
BMI1	transcription regulator	3.55E-04
MYC	transcription regulator	1.08E-03
SIRT1	transcription regulator	1.25E-03
TBPL1	transcription regulator	1.27E-03
CEBPZ	transcription regulator	2.07E-02
NUPR1	transcription regulator	4.39E-03
HNF1A	transcription regulator	5.07E-03
TP53	transcription regulator	5.70E-03
PIAS3	transcription regulator	8.39E-03
SPDEF	transcription regulator	9.80E-03
CCND1	transcription regulator	1.10E-02
E2F4	transcription regulator	1.13E-02
STAT1	transcription regulator	2.02E-02
MEF2B	transcription regulator	2.07E-02
NKX2-8	transcription regulator	2.07E-02
ERG	transcription regulator	2.34E-02
CBX3	transcription regulator	2.46E-02
MYOD1	transcription regulator	2.55E-02
EGR3	transcription regulator	2.81E-02
E2F3	transcription regulator	3.06E-02
SNAI2	transcription regulator	3.29E-02
MAX	transcription regulator	3.57E-02
YAP1	transcription regulator	3.96E-02
TEAD3	transcription regulator	4.10E-02
PLAGL2	transcription regulator	4.10E-02
GLIS2	transcription regulator	4.24E-02
SMARCB1	transcription regulator	4.58E-02
ELF1	transcription regulator	4.74E-02
PROX1	transcription regulator	4.74E-02

Table S4. Echocardiographic characteristics of WT mice 2 weeks after TAC treatment.

Group Number	Sham n=12	TAC n=12
LVDD, mm	3.55±0.31	3.59±0.29
LVDS, mm	2.32±0.24	2.38±0.32
LVPWD, mm	0.60±0.16	0.71±0.12
LVPWS, mm	0.85±0.17	1.05±0.17**
LVFS, %	34.27±3.91	36.18±5.79

LVDD: left ventricle (LV) diameter at end diastole; LVDS: LV diameter at end systole; LVPWD: LV posterior wall thickness at end diastole; LVPWS: LV posterior wall thickness at end systole; LVFS: LV fractional shortening. ***P*<0.01 TAC *versus* Sham control.

Table S5. Echocardiographic characteristics of WT mice 4 weeks after TAC treatment.

Group Number	Sham n=11	TAC n=13
LVDD, mm	3.63±0.24	3.63±0.28
LVDS, mm	2.38±0.26	2.41±0.48
LVPWD, mm	0.61±0.12	0.82±0.13***
LVPWS, mm	0.88±0.14	1.16±0.12***
LVFS, %	33.64±4.57	38.35±6.51*

LVDD: left ventricle (LV) diameter at end diastole; LVDS: LV diameter at end systole; LVPWD: LV posterior wall thickness at end diastole; LVPWS: LV posterior wall thickness at end systole; LVFS: LV fractional shortening. *P<0.05, ***P<0.001 TAC *versus* Sham control.

Table S6. Echocardiographic characteristics of WT mice 8 weeks after TAC treatment.

Group	Sham	TAC
Number	n=6	n=12
LVDD, mm	3.69±0.59	3.77±0.60
LVDS, mm	2.41±0.48	2.59±0.76
LVPWD, mm	0.63±0.07	0.77±0.11**
LVPWS, mm	0.89±0.12	1.06±0.17*
LVFS, %	33.73±6.05	30.16±8.26

LVDD: left ventricle (LV) diameter at end diastole; LVDS: LV diameter at end systole; LVPWD: LV posterior wall thickness at end diastole; LVPWS: LV posterior wall thickness at end systole; LVFS: LV fractional shortening. *P<0.05, **P<0.01 TAC *versus* Sham control.

Table S7. Echocardiographic characteristics of WT mice 2 weeks after cessation of ADR treatment.

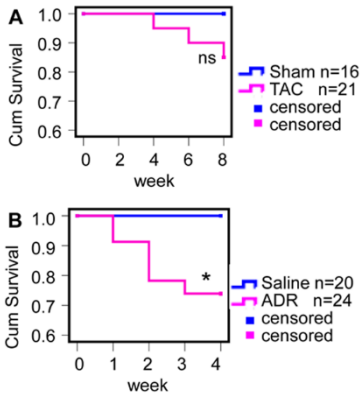
Group Number	Saline n=10	ADR n=8
LVDD, mm	3.46±0.21	3.59±0.19
LVDS, mm	2.19±0.22	2.53±0.15
LVPWD, mm	0.59±0.07	0.49±0.06**
LVPWS, mm	0.85±0.09	0.69±0.09*
SV, μl	38.18±5.92	35.12±3.32
LVFS, %	36.73±4.86	28.45±5.15**

LVDD: left ventricle (LV) diameter at end diastole; LVDS: LV diameter at end systole; LVPWD: LV posterior wall thickness at end diastole; LVPWS: LV posterior wall thickness at end systole; LVFS: LV fractional shortening; SV: stroke volume. *P<0.05, **P<0.01 ADR *versus* Saline control.

Table S8. Canonical pathways interacted with CYP2E1 screened by Co-IP-MS.

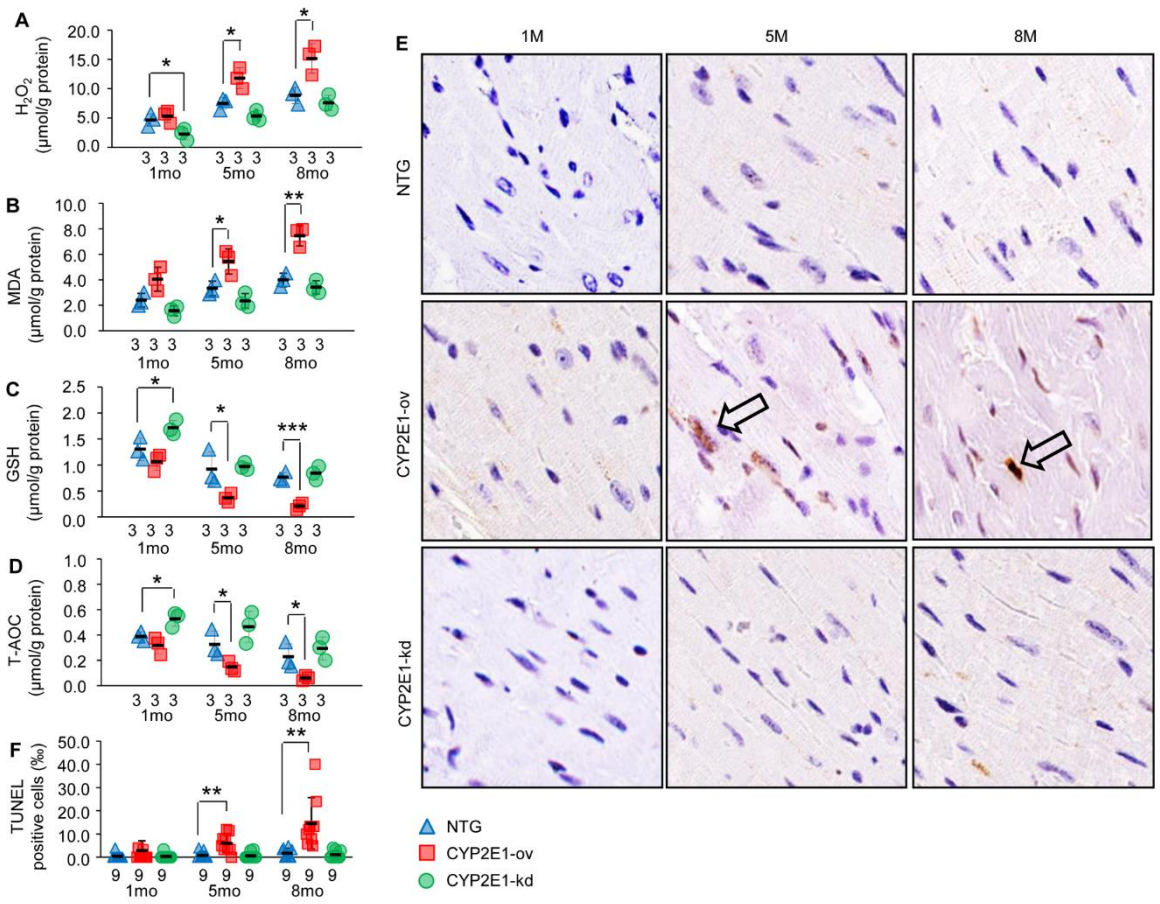
Ingenuity Canonical Pathways	-log(p-value)	Ratio
p70S6K Signaling	2.26E+00	6.06E-02
Phospholipase C Signaling	1.97E+00	4.55E-02
ERK5 Signaling	1.97E+00	7.58E-02
mTOR Signaling	1.67E+00	4.48E-02
Cardiac Hypertrophy Signaling	1.66E+00	4.26E-02
G Protein Signaling Mediated by Tubby	1.58E+00	9.38E-02
Protein Kinase A Signaling	1.46E+00	3.49E-02
PI3K Signaling	1.31E+00	4.62E-02
ERK/MAPK Signaling	1.29E+00	4.00E-02
Gαq Signaling	6.43E-01	3.11E-02
JAK/Stat Signaling	6.27E-01	3.61E-02
TGF-β Signaling	5.89E-01	3.45E-02
Apoptosis Signaling	5.62E-01	3.33E-02
SAPK/JNK Signaling	4.54E-01	2.88E-02
Wnt/Ca+ pathway	4.37E-01	3.17E-02
HGF Signaling	3.85E-01	2.61E-02
ErbB4 Signaling	3.67E-01	2.78E-02
RhoA Signaling	3.37E-01	2.42E-02
Wnt/β-catenin Signaling	3.37E-01	2.33E-02
FGF Signaling	2.58E-01	2.20E-02
Death Receptor Signaling	2.49E-01	2.15E-02
STAT3 Pathway	2.31E-01	2.06E-02
AMPK Signaling	0.00E+00	1.39E-02
PKCθ Signaling in T Lymphocytes	0.00E+00	1.89E-02
Role of MAPK Signaling in the Pathogenesis of Influenza	0.00E+00	1.39E-02

Figure S1. Cumulative percent mortality for mouse models.



A, WT-sham (*n*=16 mice) and WT-TAC (*n*=21 mice) mice was calculated every two weeks until the eighth week after TAC (non siganification *versus* TAC group). **B**, WT-saline (*n*=20 mice) and WT-ADR (*n*=24 mice) mice was calculated every week until 2 weeks after cessation of ADR treatment (**P*<0.05 *versus* saline group).

Figure S2. CYP2E1 increased oxidative stress and apoptosis in mice.



Level of H_2O_2 (**A**), malondialdehyde (MDA) (**B**), glutathione (GSH) (**C**) and total antioxidation capacity (T-AOC) (**D**) in heart tissues from NTG, CYP2E1-ov and CYP2E1-kd transgenic mice at 1, 5 and 8 months of age (* $P<0.05$, ** $P<0.01$ or *** $P<0.001$ *versus* NTG group). **E**, Representative photographs of heart tissue used for TUNEL assay. The arrows indicate TUNEL-positive cells (magnification, ×400). **F**, The quantitative analysis of apoptotic cells in the hearts tissues from NTG, CYP2E1-ov and CYP2E1-kd transgenic mice at 1, 5 and 8 months of age (n=3 mice per group, n=3 microscopic fields per mice, ** $P<0.01$ *versus* NTG group).