

Supplementary Information

Loss of NR2E3 represses AHR by LSD1 reprogramming, is associated with poor prognosis in liver cancer

Tilak Khanal¹, Kwangmin Choi², Yuet-Kin Leung^{1,4,5}, Jiang Wang³, Dasom Kim¹, Vinothini Janakiram^{1,4}, Sung-Gook Cho⁴, Alvaro Puga^{1,4}, Shuk-Mei Ho^{1,4,5,7} and Kyoungyun Kim^{1,4*}

¹ Department of Environmental Health, University of Cincinnati, College of Medicine, 160 Panzeca way., Cincinnati, OH 45267

² Division of Experimental Hematology and Cancer Biology, Cincinnati Children's Hospital medical Center, Cincinnati, OH 45229

³ Department of Pathology and Laboratory Medicine, University of Cincinnati, College of Medicine, 231 Albert Sabin Way., Cincinnati, OH 45267

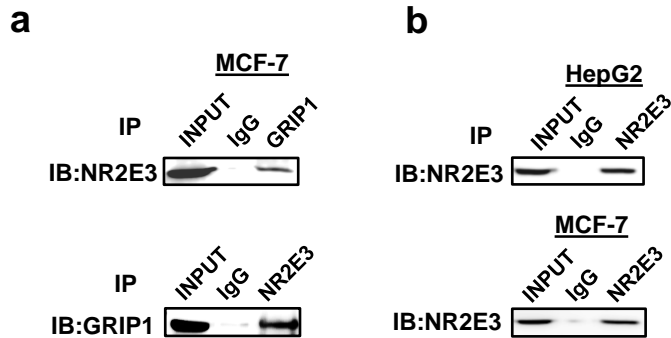
⁴ Center for Environmental Genetics (*P30 ES006096*), University of Cincinnati, College of Medicine, 160 Panzeca way., Cincinnati, OH 45267

⁵ Cincinnati Cancer Center, 231 Albert Sabin Way, Cincinnati, OH 45267

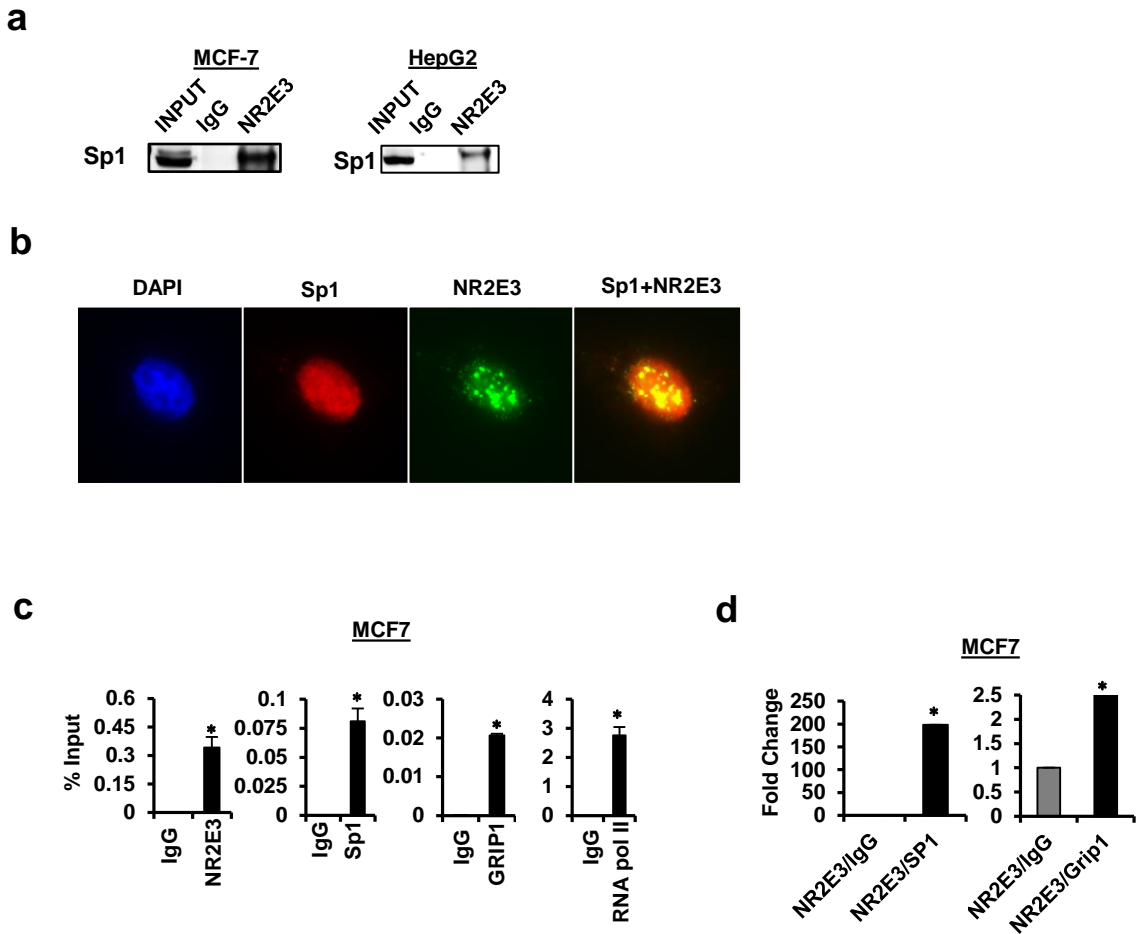
⁶ Department of Biotechnology, Korea National University of Transportation, Chung-ju, South Korea.

⁷ Cincinnati VA Medical Center, 3200 Vine Street, Cincinnati, OH 45220

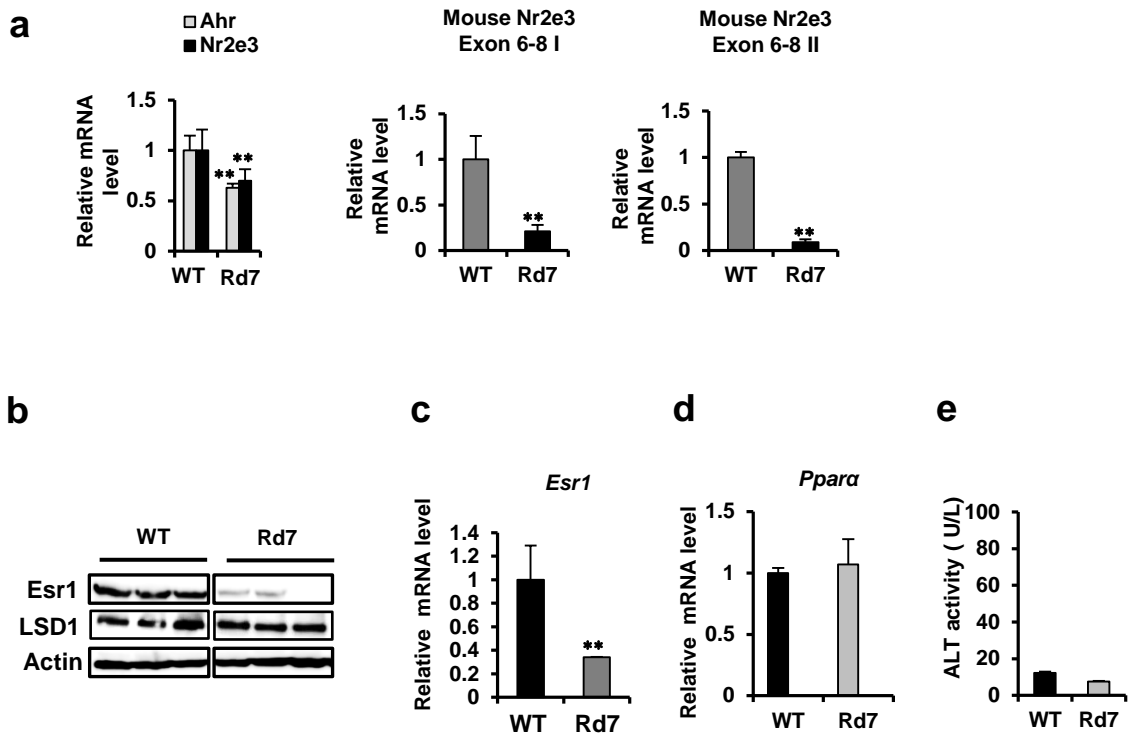
Correspondence and requests for materials should be addressed to K.K. (email:kim2ku@uc.edu)



Supplementary Figure 1. NR2E3-GRIP1 interaction in MCF-7 human breast cancer cells and evaluation of anti-NR2E3 antibodies. (a) Co-Immunoprecipitation (IP) assay was performed to confirm NR2E3-GRIP1 interaction in MCF-7 cells. Anti-NR2E3 antibody (sc-374513), anti-Grip1 antibody or control non-immune IgG (IgG) was used for immunoprecipitation and immunoblot analysis (IB) was performed detecting GRIP1 (Top) or vice versa (Bottom). (b) To validate whether anti-NR2E3 antibody efficiently precipitates NR2E3 protein, Co-IP assays were carried out. A rabbit polyclonal anti-NR2E3 (Santa Cruz Biotech, Cat#: sc-292264) was used for pulling down NR2E3 protein either from HepG2 (Top) or MCF-7 whole cell lysate (Bottom) and then NR2E3 was detected by immunoblotting with a mouse monoclonal NR2E3 antibody (Santa Cruz Biotech, Cat #: sc-374513). Images of uncropped western blots and gels can be found in Supplementary Fig. 11.

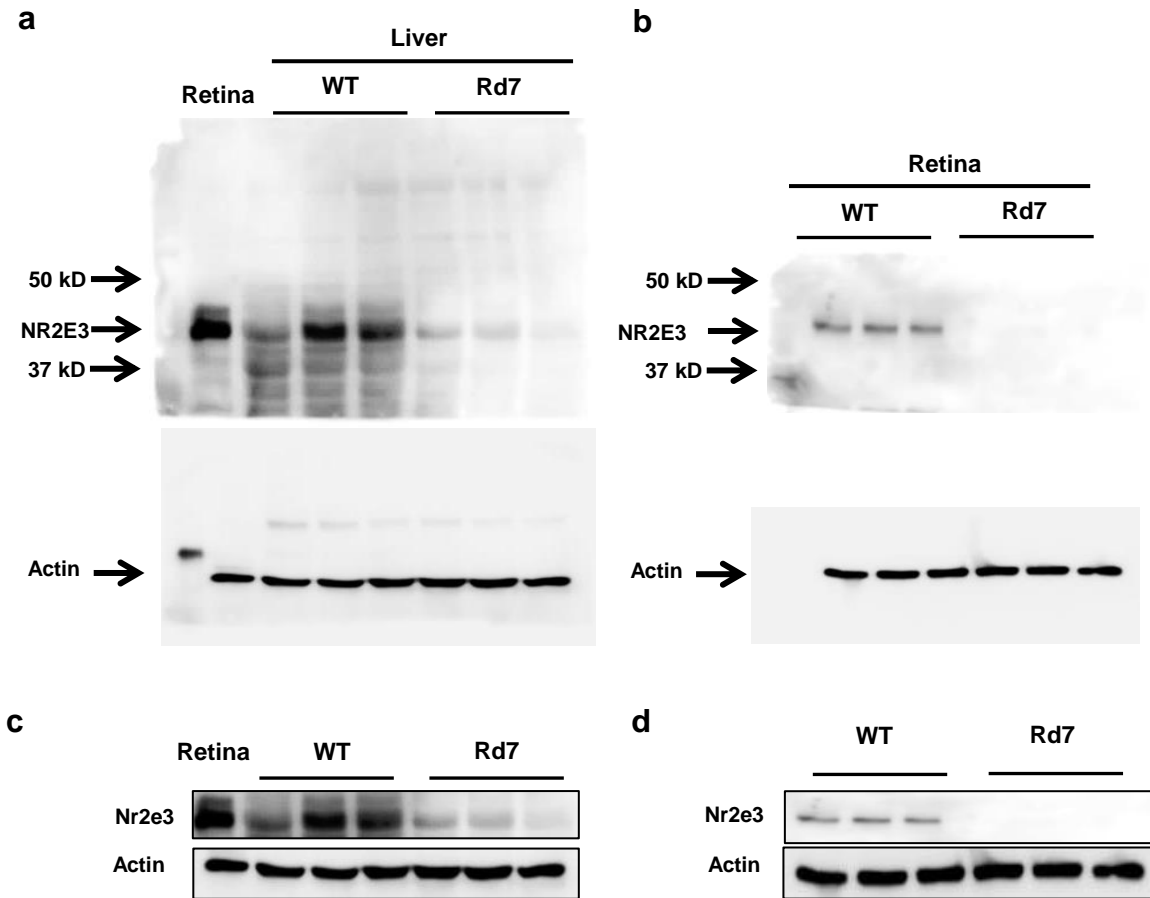


Supplementary Figure 2. The formation of NR2E3-mediated transcriptionally active complex with Sp1 and GRIP1 on the AHR gene promoter in MCF-7 cells. (a) Sp1 was co-immunoprecipitated with NR2E3 using MCF-7 cell lysate. (b) The nuclear co-localization of NR2E3 (green) with Sp1 (red) in HepG2 cells as shown as yellow speckles. (c) Binding of NR2E3, Sp1, GRIP1 and RNA pol II to the proximal promoter region of AHR gene in MCF7 cells as determined by ChIP-PCR. (d) Re-ChIP PCR results indicates the formation of NR2E3/Sp1 and NR2E3/ GRIP1 protein complex in the AHR proximal promoter region in MCF7 cells. Results are means \pm SE for at least 3 replicated determinations, and significantly ($P < .05$) increased (*) responses are indicated. Images of uncropped western blots and gels can be found in Supplementary Fig. 11.

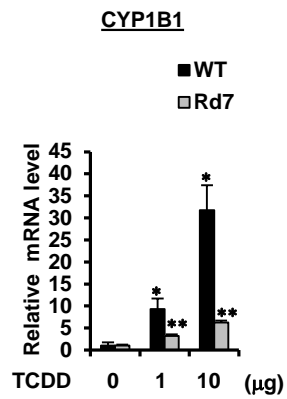


Supplementary Figure 3. Effects of NR2E3 depletion on the level of Nr2e3, Esr1 and other Ahr target gene expressions and liver damage *in vivo*. (a) Changes in mRNA levels of Nr2e3 and Ahr in Rd7 mice was determined by qRT-PCR analysis using the primer set amplifying Ahr and three primer sets amplifying different regions of Nr2e3 gene [Nr2e3, *Nr2e3* Exon6-8 I and *Nr2e3* Exon 6-8 II]. (b) The livers were homogenized, and the ER protein levels were analyzed on immunoblots of cell lysates probed with anti-ER and anti-LSD1 antibodies. (c-d) The livers were homogenized and lysed, and the total RNA was prepared for the PCR analysis of *Esr1* and *Ppara* mRNA expression relative to the GAPDH expression. (e) Measurement of alanine aminotransferase (ALT) activity, a indicator of liver damage, using serum from wild type and Rd7 mice. Results are means \pm SE for at least 3 replicated determinations, and significantly ($P < .05$) decreased (**) response is indicated. Images of uncropped western blots and gels can be found in Supplementary Fig. 11.

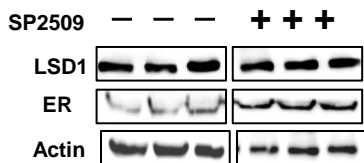
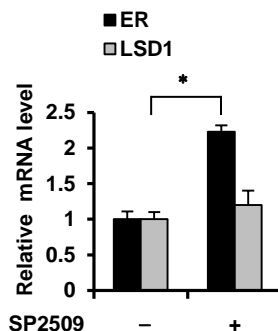
Anti-NR2E3 antibody (Abcam, Cat #172542)



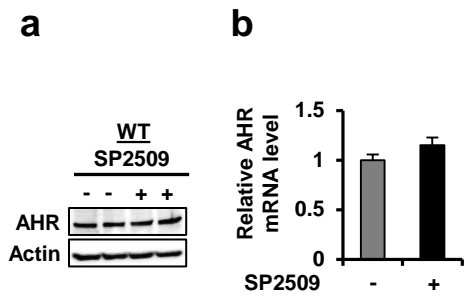
Supplementary Figure 4. *Nr2e3* protein expression in the liver and retina of Rd7 mice. (a) The original blot image for Nr2e3 protein detection in the liver of WT and Rd7 mice using C57/BL6 mouse retina lysate (Zyagen, Inc., Cat# MT-106-C57) as positive control. (b) Nr2e3 protein levels were also detected using retina lysate extracted from WT and Rd7 mice. In each lane, 30-50 μ g of total protein lysate was loaded. Nr2e3 protein band was detected with NR2E3 antibody (Abcam, Cat # ab172542). The control beta-actin bands were shown down below (c, d). *Nr2e3* proteins were expressed low in the liver but not the retina of Rd7 mice.



Supplementary Figure 5. Effects of NR2E3 loss on the induction level of CYP1B1 in RD7 mice after TCDD treatment *in vivo*. The induction levels of CYP1B1 mRNA was significantly reduced in Rd7 mice. Results are means \pm SE for at least 3 replicated determinations, and significantly ($P < .05$) increased (*) or attenuated (**) responses are indicated.

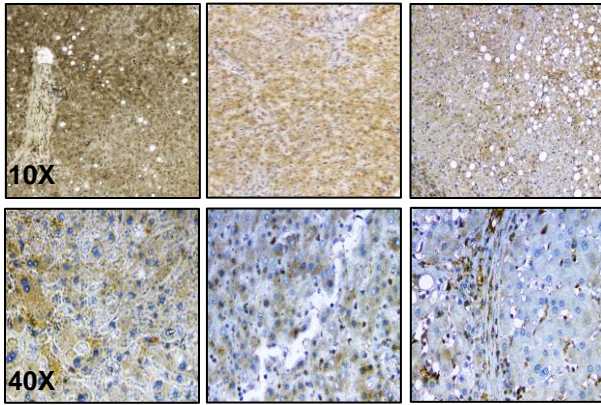
a**b**

Supplementary Figure 6. Effects of LSD1 inhibitor treatment on AHR expression. (a) The livers were homogenized, and the LSD1 and ER protein levels were analyzed on immunoblots of cell lysates probed with anti-LSD1 and anti-ER antibodies. (b) The livers were homogenized and lysed, and the total RNA was prepared for the PCR analysis of LSD1 and ER mRNA expression relative to the GAPDH expression. Results are means \pm SE for at least 3 replicated determinations, and significantly ($P < .05$) increased (*) response is indicated. Images of uncropped western blots and gels can be found in Supplementary Fig. 11.

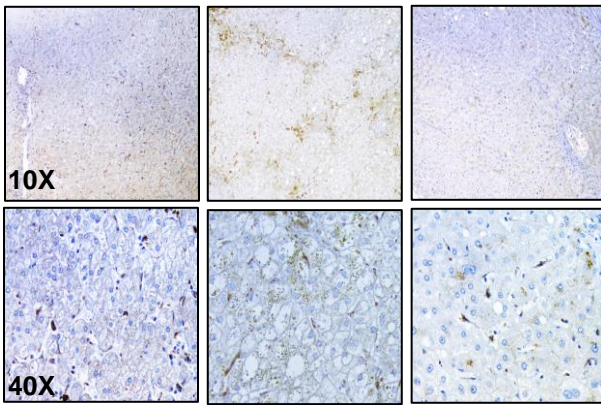


Supplementary Figure 7. Effects of LSD1 inhibitor treatment on AHR expression in wild type mice. (a) Wild type mouse livers treated with and without SP2509 were homogenized, and the AHR protein levels were analyzed on immunoblots of cell lysates probed with anti-AHR antibodies. (b) The livers were homogenized and lysed, and the total RNA was prepared for the PCR analysis of NR2E3 and AHR mRNA expression relative to the GAPDH expression. Images of uncropped western blots and gels can be found in Supplementary Fig. 11.

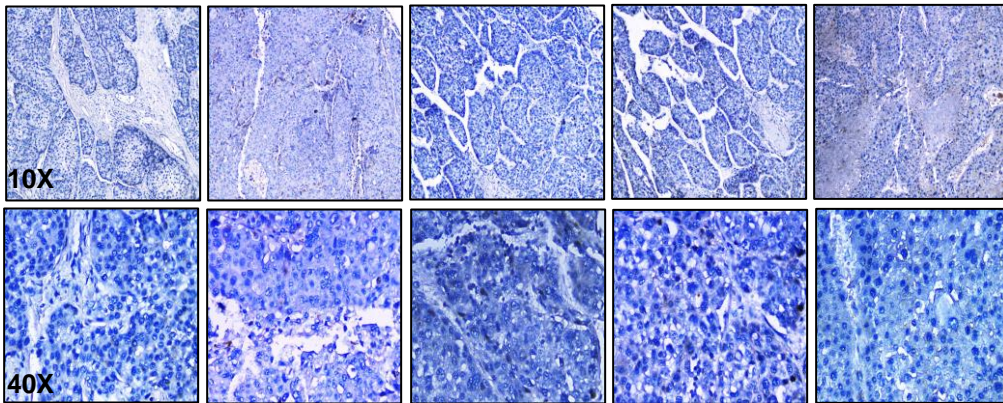
Normal Liver



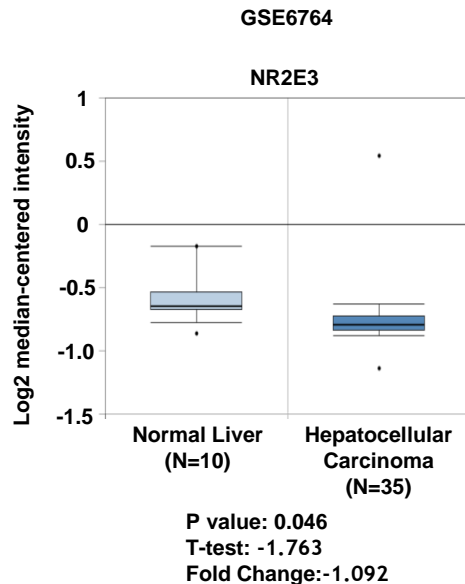
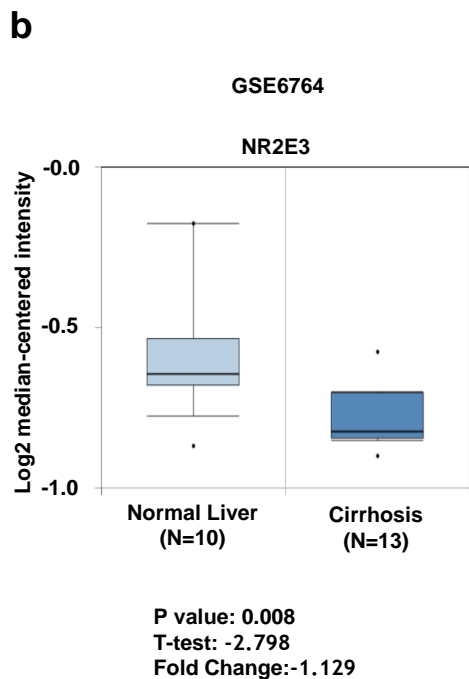
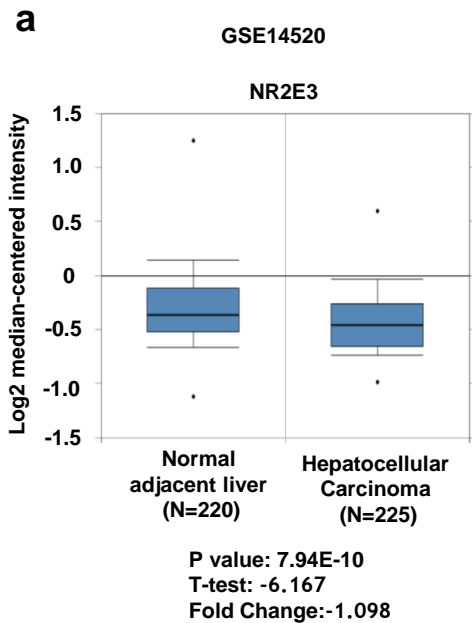
Cirrhosis



Liver Tumor



Supplementary Figure 8. Representative Images for immunostaining of NR2E3 in normal, cirrhotic and tumor tissues (10X and 40X magnification).



Supplementary Figure 9. Expression levels of NR2E3 mRNAs in normal, cirrhotic and hepatocellular carcinoma in two independent clinical GEO data sets . (a) NR2E3 levels were decreased in human hepatocellular carcinoma patient samples (GEO1452). (b) Reduced NR2E3 levels were detected in cirrhotic (b, left) and hepatocellular carcinoma (b, right) (GSE6764).

Supplementary Table 1. Major signaling pathways that are significantly associated with down-regulated gene signature induced by NR2E3 deletion in HepG2 cells.

NAME	SIZE	ES	NES	NOM p-val	FDR q-val	FWER p-val
KEGG_DNA_REPLICATION	36	-0.587	-4.185	0.000	0.000	0.000
KEGG_CELL_CYCLE	121	-0.318	-4.040	0.000	0.000	0.000
KEGG_COMPLEMENT_AND_COAGULATION_CASCADES	60	-0.403	-3.773	0.000	0.000	0.000
KEGG_NUCLEOTIDE_EXCISION_REPAIR	44	-0.412	-3.295	0.000	0.000	0.000
KEGG_STARCH_AND_SUCROSE_METABOLISM	45	-0.403	-3.239	0.000	0.000	0.000
KEGG_HOMOLOGOUS_RECOMBINATION	28	-0.504	-3.162	0.000	0.000	0.000
KEGG_DRUG_METABOLISM_CYTOCHROME_P450	55	-0.359	-3.107	0.000	0.000	0.000
KEGG_PROPANOATE_METABOLISM	30	-0.465	-3.050	0.000	0.000	0.000
KEGG_HUNTINGTONS_DISEASE	160	-0.210	-3.048	0.000	0.000	0.000
KEGG_MISMATCH_REPAIR	23	-0.527	-3.047	0.000	0.000	0.000
KEGG_METABOLISM_OF_XENOBIOTICS_BY_CYTOCHROME_P450	58	-0.335	-3.021	0.000	0.000	0.000
KEGG_FATTY_ACID_METABOLISM	35	-0.424	-2.962	0.000	0.000	0.000
KEGG_ALANINE_ASPARTATE_AND_Glutamate_METABOLISM	29	-0.425	-2.686	0.000	0.000	0.001
KEGG_ALZHEIMERS_DISEASE	142	-0.194	-2.688	0.000	0.000	0.001
KEGG_CITRATE_CYCLE_TCA_CYCLE	29	-0.411	-2.715	0.000	0.000	0.001
KEGG_LYSINE_DEGRADATION	43	-0.352	-2.745	0.000	0.000	0.001
KEGG_OOCYTE_MEIOSIS	100	-0.241	-2.795	0.000	0.000	0.001
KEGG_SPLICEOSOME	121	-0.218	-2.841	0.000	0.000	0.001
KEGG_PYRIMIDINE_METABOLISM	94	-0.257	-2.847	0.000	0.000	0.001
KEGG_STEROID_HORMONE_BIOSYNTHESIS	45	-0.354	-2.856	0.000	0.000	0.001
KEGG_N_GLYCAN_BIOSYNTHESIS	46	-0.356	-2.867	0.000	0.000	0.001
KEGG_OXIDATIVE_PHOSPHORYLATION	108	-0.239	-2.876	0.000	0.000	0.001
KEGG_VALINE_LEUCINE_AND_Isoleucine_DEGRADATION	44	-0.340	-2.634	0.000	0.000	0.003
KEGG_PEROXISOME	75	-0.259	-2.603	0.000	0.000	0.005
KEGG_PENTOSE_AND_Glucuronate_INTERCONVERSIONS	26	-0.422	-2.537	0.000	0.000	0.008
KEGG_PARKINSONS_DISEASE	102	-0.217	-2.528	0.000	0.000	0.009
KEGG_PROGESTERONE_MEDIATED_OOCYTE_MATURATION	75	-0.238	-2.440	0.002	0.001	0.022
KEGG_SYSTEMIC_LUPUS_ERYTHEMATOSUS	86	-0.227	-2.451	0.000	0.001	0.022
KEGG_BASE_EXCISION_REPAIR	33	-0.349	-2.400	0.000	0.001	0.028
KEGG_PURINE_METABOLISM	139	-0.175	-2.404	0.000	0.001	0.028
KEGG_ASCORBATE_AND_ALDARATE_METABOLISM	24	-0.410	-2.387	0.000	0.001	0.031
KEGG_RETINOL_METABOLISM	43	-0.294	-2.344	0.000	0.002	0.040
KEGG_PPAR_SIGNALING_PATHWAY	55	-0.268	-2.340	0.002	0.002	0.042
KEGG_PROXIMAL_TUBULE_BICARBONATE_RECLAMATION	21	-0.421	-2.300	0.000	0.002	0.056
KEGG_DRUG_METABOLISM_OTHER_ENZYMES	45	-0.282	-2.288	0.000	0.002	0.060
KEGG_Glutathione_METABOLISM	47	-0.277	-2.235	0.000	0.003	0.084
KEGG_PENTOSE_PHOSPHATE_PATHWAY	23	-0.370	-2.202	0.000	0.004	0.108
KEGG_GLYCOLYSIS_Gluconeogenesis	50	-0.262	-2.154	0.004	0.005	0.145
KEGG_LYSOSOME	113	-0.168	-2.096	0.000	0.008	0.210
KEGG_BIOSYNTHESIS_OF_UNSATURATED_FATTY_ACIDS	22	-0.378	-2.071	0.000	0.009	0.245
KEGG_PRIMARY_BILE_ACID_BIOSYNTHESIS	12	-0.481	-2.013	0.002	0.012	0.335
KEGG_ARGININE_AND_PROLINE_METABOLISM	51	-0.235	-1.973	0.010	0.016	0.411
KEGG_BUTANOATE_METABOLISM	32	-0.289	-1.975	0.000	0.016	0.408
KEGG_P53_SIGNALING_PATHWAY	65	-0.184	-1.767	0.014	0.047	0.818
KEGG_BETA_ALANINE_METABOLISM	21	-0.329	-1.771	0.018	0.047	0.808

Supplementary Table 2. Major signaling pathways that are significantly associated with up-regulated gene signature induced by NR2E3 deletion in HepG2 cells.

NAME	ES	NES	NOM p-val	FDR q-val	FWER p-val
KEGG_ENDOCYTOSIS	0.2388	3.5523	0.0000	0.0000	0.0000
KEGG_MAPK_SIGNALING_PATHWAY	0.1770	3.0455	0.0000	0.0000	0.0000
KEGG_RIG_I_LIKE_RECEPTOR_SIGNALING_PATHWAY	0.3143	2.5944	0.0000	0.0028	0.0110
KEGG_EPITHELIAL_CELL_SIGNALING_IN_HELICOBACTER_PYLORI_INFECTION	0.2543	2.4216	0.0000	0.0056	0.0280
KEGG_PATHWAYS_IN_CANCER	0.1180	2.3296	0.0000	0.0083	0.0530
KEGG_HYPERTROPHIC_CARDIOMYOPATHY_HCM	0.2553	2.2701	0.0000	0.0117	0.0860
KEGG_SMALL_CELL_LUNG_CANCER	0.2225	2.2420	0.0000	0.0121	0.1010
KEGG_JAK_STAT_SIGNALING_PATHWAY	0.1867	2.2072	0.0020	0.0122	0.1300
KEGG_CYTOKINE_CYTOKINE_RECEPTOR_INTERACTION	0.1502	2.2093	0.0000	0.0134	0.1280
KEGG_NEUROACTIVE_LIGAND_RECEPTOR_INTERACTION	0.1621	2.1049	0.0021	0.0197	0.2210
KEGG_CIRCADIAN_RHYTHM_MAMMAL	0.4645	2.0350	0.0041	0.0278	0.3260
KEGG_RIBOSOME	0.1855	1.9918	0.0082	0.0325	0.4020
KEGG_APOPTOSIS	0.1926	1.9747	0.0060	0.0330	0.4330
KEGG_REGULATION_OF_ACTIN_CYTOSKELETON	0.1286	1.9559	0.0099	0.0337	0.4650
KEGG_REGULATION_OF_AUTOPHAGY	0.3494	1.8318	0.0157	0.0571	0.7240
KEGG_NEUROTROPHIN_SIGNALING_PATHWAY	0.1521	1.8404	0.0141	0.0580	0.7060
KEGG_FOCAL_ADHESION	0.1257	1.8475	0.0121	0.0597	0.6940
KEGG_HEMATOPOIETIC_CELL_LINEAGE	0.2074	1.7542	0.0176	0.0810	0.8500
KEGG_SNARE_INTERACTIONS_IN_VESICULAR_TRANSPORT	0.2423	1.7406	0.0237	0.0819	0.8670
KEGG_TYPE_II_DIABETES_MELLITUS	0.2457	1.6798	0.0309	0.1055	0.9310
KEGG_DILATED_CARDIOMYOPATHY	0.1705	1.6508	0.0395	0.1166	0.9600
KEGG_ARRHYTHMOGENIC_RIGHT_VENTRICULAR_CARDIOMYOPATHY_ARVC	0.1857	1.5860	0.0450	0.1504	0.9880
KEGG_NATURAL_KILLER_CELL_MEDIATED_CYTOTOXICITY	0.1414	1.5713	0.0464	0.1543	0.9920

Supplementary Table 3. Common 252 genes regulated by NR2E3 deletion in both MCF-7 and HepG2 cells.

SYMBOL	Description	MCF-7		HepG2	
		Fold Change	P value	Fold Change	P value
ABLIM1	actin binding LIM protein 1	2.17	6.77E-09	0.49	9.99E-18
ACOT9	acyl-CoA thioesterase 9	1.47	6.87E-05	1.83	8.29E-08
ACTA2	actin, alpha 2, smooth muscle, aorta	1.85	2.01E-07	0.66	2.49E-05
ADAR	adenosine deaminase, RNA-specific	0.98	8.59E-01	0.71	3.09E-05
ADCY9	adenylate cyclase 9	0.71	3.21E-04	0.72	4.63E-04
ADD3	adducin 3 (gamma)	0.70	7.09E-05	0.59	1.14E-07
AHR	aryl hydrocarbon receptor	0.61	1.08E-04	0.65	8.23E-06
AIF1L	allograft inflammatory factor 1-like	0.70	2.50E-04	0.28	2.04E-17
AK4	adenylate kinase 4	0.52	7.92E-08	0.44	3.18E-20
AKR1B10	aldo-keto reductase family 1, member B10 (aldose reductase)	1.43	1.53E-04	0.50	6.60E-09
AKR1D1	aldo-keto reductase family 1, member D1	0.58	1.67E-06	0.26	1.55E-07
ALDH3A2	aldehyde dehydrogenase 3 family, member A2	0.63	6.59E-05	0.54	4.43E-12
ALDH4A1	aldehyde dehydrogenase 4 family, member A1	0.56	2.19E-07	0.47	9.29E-17
ANKRD1	ankyrin repeat domain 1 (cardiac muscle)	1.52	1.24E-04	4.76	6.94E-89
ANKRD13D	ankyrin repeat domain 13 family, member D	0.70	1.64E-04	1.91	2.83E-04
ANTXR1	anthrax toxin receptor 1	0.66	4.22E-05	0.14	3.59E-51
ANXA1	annexin A1	5.27	1.48E-13	3.55	4.52E-14
ANXA3	annexin A3	1.76	2.12E-06	2.39	2.24E-19
AP4B1	adaptor-related protein complex 4, beta 1 subunit	0.70	4.48E-04	3.53	2.77E-09
ARHGD1B	Rho GDP dissociation inhibitor (GDI) beta	1.44	1.56E-04	17.96	1.61E-11
ASS1	argininosuccinate synthase 1	1.71	1.71E-06	0.47	6.62E-10
AXIN2	axin 2	0.59	1.34E-06	0.35	6.22E-20
B2M	beta-2-microglobulin	1.89	6.48E-08	0.72	3.68E-05
BCAS4	breast carcinoma amplified sequence 4	1.54	1.31E-05	2.71	3.33E-06
BCL2L13	BCL2-like 13 (apoptosis facilitator)	1.49	3.26E-05	1.56	4.11E-05
BHLHE41	basic helix-loop-helix family, member e41	0.59	1.83E-06	5.36	1.66E-13
BIRC3	baculoviral IAP repeat containing 3	1.80	3.26E-07	3.66	4.52E-23
BLOC1S6	biogenesis of lysosomal organelles complex-1, subunit 6, pallidin	0.61	3.50E-06	0.62	3.49E-05
BLZF1	basic leucine zipper nuclear factor 1	0.66	2.70E-05	2.41	2.95E-04
BMPR2	bone morphogenetic protein receptor, type II (serine/threonine kinase)	0.66	3.96E-05	0.51	1.58E-12
BNIP3L	BCL2/adenovirus E1B 19kDa interacting protein 3-like	0.67	3.65E-05	1.59	5.22E-08
BRI3BP	BRI3 binding protein	0.50	1.49E-08	0.23	3.49E-14
BTG3	BTG family, member 3	1.53	1.31E-05	2.12	7.82E-09
BZW1	basic leucine zipper and W2 domains 1	0.66	2.59E-04	1.34	4.33E-04
C15orf48	chromosome 15 open reading frame 48	3.12	2.30E-10	17.86	6.66E-06
C1orf116	chromosome 1 open reading frame 116	1.59	5.12E-06	5.29	1.00E-24
CADM1	cell adhesion molecule 1	0.60	1.34E-05	0.27	1.13E-46
CASP6	caspace 6, apoptosis-related cysteine peptidase	0.73	4.37E-04	0.53	2.00E-04
CBL	Cbl proto-oncogene, E3 ubiquitin protein ligase	1.55	1.86E-04	1.59	2.35E-06
CCDC92	coiled-coil domain containing 92	0.60	8.68E-06	1.81	2.00E-05
CCNB1IP1	cyclin B1 interacting protein 1, E3 ubiquitin protein ligase	1.51	2.44E-05	1.87	1.95E-11
CD44	CD44 molecule (Indian blood group)	0.52	5.75E-08	8.72	1.45E-08
CD68	CD68 molecule	0.50	6.78E-08	2.02	4.23E-06
CDA	cytidine deaminase	7.63	3.88E-13	9.40	4.53E-44
CDC16	cell division cycle 16	0.67	1.78E-04	1.51	1.20E-04
CDCA7	cell division cycle associated 7	0.67	9.88E-05	0.26	7.37E-21
CDKN1A	cyclin-dependent kinase inhibitor 1A (p21, Cip1)	1.67	2.80E-06	2.18	3.23E-23
CFB	complement factor B	2.85	3.53E-11	0.35	1.17E-32
CHRNA5	cholinergic receptor, nicotinic, alpha 5 (neuronal)	0.68	1.23E-04	1.93	2.41E-05
CHRNB1	cholinergic receptor, nicotinic, beta 1 (muscle)	1.71	2.11E-06	1.83	2.83E-07
COL18A1	collagen, type XVIII, alpha 1	0.69	9.36E-05	0.61	2.95E-09
COMT	catechol-O-methyltransferase	0.67	5.04E-05	0.49	1.60E-11
COQ7	coenzyme Q7 homolog, ubiquinone (yeast)	0.74	4.17E-04	0.49	1.61E-06
CRCP	CGRP receptor component	0.66	1.41E-04	1.98	2.09E-07
CREBRF	CREB3 regulatory factor	1.50	8.79E-05	3.36	4.14E-24
CREG1	cellular repressor of E1A-stimulated genes 1	0.69	3.29E-04	0.44	3.75E-06
CSRNP1	cysteine-serine-rich nuclear protein 1	0.61	2.91E-05	3.15	3.31E-24
CTGF	connective tissue growth factor	0.61	1.27E-05	1.69	1.54E-10

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SYMBOL	Description	MCF-7		HepG2	
		Fold Change	P value	Fold Change	P value
CTPS2	CTP synthase 2	0.72	4.10E-04	0.35	2.25E-16
CTSB	cathepsin B	0.61	3.91E-06	1.83	5.11E-16
CUL4A	cullin 4A	0.70	3.08E-04	1.40	1.26E-04
CXCL8	chemokine (C-X-C motif) ligand 8	2.72	1.73E-10	21.01	1.10E-197
CXCR4	chemokine (C-X-C motif) receptor 4	0.57	9.12E-07	20.12	1.12E-100
CYB5A	cytochrome b5 type A (microsomal)	1.58	1.39E-04	0.45	2.75E-14
CYP1A1	cytochrome P450, family 1, subfamily A, polypeptide 1	1.57	1.34E-05	1.88	7.49E-07
DAPK3	death-associated protein kinase 3	1.47	3.96E-05	2.08	1.52E-14
DDB2	damage-specific DNA binding protein 2, 48kDa	1.62	6.33E-06	0.69	3.45E-04
DDIT3	DNA-damage-inducible transcript 3	1.79	3.17E-07	10.73	2.36E-36
DHRS2	dehydrogenase/reductase (SDR family) member 2	1.43	9.13E-05	0.58	7.79E-10
DNAJB6	DnaJ (Hsp40) homolog, subfamily B, member 6	0.66	4.22E-05	2.48	5.98E-26
DRAM1	DNA-damage regulated autophagy modulator 1	1.46	9.75E-05	0.44	4.66E-06
E2F2	E2F transcription factor 2	0.62	8.30E-06	0.35	5.21E-05
EDN1	endothelin 1	1.59	1.25E-05	3.19	3.32E-11
EGLN3	egl-9 family hypoxia-inducible factor 3	0.74	3.66E-04	3.57	6.13E-09
EIF2AK2	eukaryotic translation initiation factor 2-alpha kinase 2	2.71	1.43E-08	1.58	3.85E-04
ERBB3	v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 3	0.65	2.52E-05	0.23	3.94E-62
ERP27	endoplasmic reticulum protein 27	2.46	2.98E-09	0.15	1.34E-30
ERF1	ERBB receptor feedback inhibitor 1	1.44	9.70E-05	1.99	1.11E-18
FAH	fumarylacetoacetate hydrolase (fumarylacetoacetase)	1.48	3.42E-05	0.61	1.70E-05
FAM178A	family with sequence similarity 178, member A	0.67	3.03E-04	0.28	8.29E-30
FAM217B	family with sequence similarity 217, member B	0.70	1.45E-04	0.62	2.64E-04
FAM3C	family with sequence similarity 3, member C	0.64	1.08E-04	1.95	5.49E-06
FAM46A	family with sequence similarity 46, member A	0.70	9.94E-05	1.99	1.36E-10
FAM73A	family with sequence similarity 73, member A	0.61	1.19E-05	1.56	2.11E-04
FAT1	FAT atypical cadherin 1	0.59	2.34E-06	0.72	1.46E-05
FBXO32	F-box protein 32	1.41	1.17E-04	14.52	1.75E-26
FKBP4	FK506 binding protein 4, 59kDa	0.67	3.57E-05	2.24	2.73E-09
FKTN	fukutin	0.68	1.91E-04	0.45	2.48E-07
FOSB	FBJ murine osteosarcoma viral oncogene homolog B	0.56	2.19E-06	25.89	1.30E-95
FTH1P3	ferritin, heavy polypeptide 1 pseudogene 3	1.54	2.28E-04	1.38	4.98E-05
GABARAPL1	GABA(A) receptor-associated protein like 1	1.70	1.08E-06	3.91	2.64E-38
GADD45A	growth arrest and DNA-damage-inducible, alpha	2.01	1.41E-08	3.53	5.10E-29
GAMT	guanidinoacetate N-methyltransferase	1.38	3.19E-04	0.53	1.26E-04
GDAP1	ganglioside induced differentiation associated protein 1	0.72	3.76E-04	0.34	9.54E-05
GDF15	growth differentiation factor 15	4.43	9.89E-14	2.81	2.76E-37
GJC1	gap junction protein, gamma 1, 45kDa	0.70	2.85E-04	4.76	6.72E-36
GOLT1A	golgi transport 1A	1.47	2.44E-04	3.78	5.62E-19
GPD1L	glycerol-3-phosphate dehydrogenase 1-like	0.63	2.25E-05	0.36	4.98E-16
GP1R	G protein-coupled estrogen receptor 1	0.58	6.83E-07	0.54	7.92E-05
GPX3	glutathione peroxidase 3 (plasma)	0.65	8.62E-05	0.27	8.00E-48
GRAMD3	GRAM domain containing 3	1.48	3.98E-05	2.61	3.45E-11
GRB7	growth factor receptor-bound protein 7	1.53	3.61E-05	0.43	2.28E-10
GTF2H1	general transcription factor IIH, polypeptide 1, 62kDa	0.69	8.22E-05	1.62	2.32E-05
GTF2IP1	general transcription factor Iii, pseudogene 1	0.68	1.41E-04	0.47	2.56E-08
HCFC1R1	host cell factor C1 regulator 1 (XPO1 dependent)	1.89	7.32E-05	1.75	8.81E-05
HLA-G	major histocompatibility complex, class I, G	1.49	1.43E-04	2.32	3.63E-04
HMGA1	high mobility group AT-hook 1	1.53	5.68E-05	2.81	1.57E-31
HMGB1	high mobility group box 1	0.68	1.47E-04	0.52	1.16E-14
HMGB3	high mobility group box 3	0.71	1.47E-04	0.32	7.58E-18
HMOX1	heme oxygenase (decycling) 1	2.39	3.92E-08	10.44	8.60E-55
HNMT	histamine N-methyltransferase	1.81	9.75E-04	0.45	3.63E-14
HNRNPA1P10	heterogeneous nuclear ribonucleoprotein A1 pseudogene 10	0.72	4.42E-04	0.35	3.35E-42
HNRNPAB	heterogeneous nuclear ribonucleoprotein A/B	0.64	1.48E-05	0.33	2.56E-33
HRK	harakiri, BCL2 interacting protein	1.52	2.55E-04	20.88	5.49E-10
HSH2D	hematopoietic SH2 domain containing	1.50	3.83E-05	3.76	2.10E-05
HSPA12A	heat shock 70kDa protein 12A	0.71	1.27E-04	0.58	3.34E-04

Supplementary Table 3. Common 252 genes regulated by NR2E3 deletion in both MCF-7 and HepG2 cells.

SYMBOL	Description	MCF-7		HepG2	
		Fold Change	P value	Fold Change	P value
HYAL1	hyaluronoglucosaminidase 1	1.53	1.72E-05	0.61	3.77E-06
ID2	inhibitor of DNA binding 2, dominant negative helix-loop-helix protein	0.71	1.81E-04	0.37	2.69E-30
IFITM3	interferon induced transmembrane protein 3	4.64	6.49E-10	0.67	6.72E-05
IFNAR1	interferon (alpha, beta and omega) receptor 1	0.56	1.84E-06	0.67	2.04E-04
IFT122	intraflagellar transport 122	0.64	7.80E-06	0.53	8.70E-05
IGSF1	immunoglobulin superfamily, member 1	1.57	5.27E-06	0.53	5.24E-09
IL17RB	interleukin 17 receptor B	0.62	1.09E-05	0.52	3.47E-10
IL17RD	interleukin 17 receptor D	0.60	3.55E-06	2.55	2.51E-06
IL18	interleukin 18	0.58	3.53E-06	3.37	3.04E-36
INHBB	inhibin, beta B	1.67	1.82E-05	0.63	3.75E-05
INTS6	integrator complex subunit 6	0.72	2.48E-04	1.43	4.05E-04
IRF9	interferon regulatory factor 9	6.53	2.47E-15	2.11	1.03E-06
ITGA5	integrin, alpha 5 (fibronectin receptor, alpha polypeptide)	1.47	1.05E-04	21.12	6.85E-137
JAK2	Janus kinase 2	0.74	3.73E-04	1.91	7.93E-05
KIAA0513	KIAA0513	1.78	1.42E-06	3.19	2.74E-11
KIF15	kinesin family member 15	0.67	1.56E-04	0.29	9.77E-15
KLF2	Kruppel-like factor 2	0.60	4.25E-06	33.57	8.83E-11
KRT15	keratin 15	0.60	1.13E-05	21.77	2.35E-57
KRT80	keratin 80	1.81	3.35E-06	1.49	5.01E-06
LAMC2	laminin, gamma 2	1.37	2.79E-04	82.68	1.44E-21
LCP1	lymphocyte cytosolic protein 1 (L-plastin)	2.13	6.55E-09	5.32	3.21E-33
LMCD1	LIM and cysteine-rich domains 1	1.68	3.17E-06	2.33	8.75E-13
MACF1	microtubule-actin crosslinking factor 1	0.71	4.79E-04	1.71	4.78E-12
MALT1	mucosa associated lymphoid tissue lymphoma translocation gene 1	0.73	4.59E-04	0.49	1.09E-11
MB21D2	Mab-21 domain containing 2	1.52	3.54E-05	2.47	1.16E-04
MBD4	methyl-CpG binding domain protein 4	0.67	1.50E-04	0.62	1.22E-04
MBNL3	muscleblind-like splicing regulator 3	0.67	4.18E-05	0.18	5.59E-102
MCM10	minichromosome maintenance complex component 10	0.73	3.14E-04	0.28	6.90E-14
MCM8	minichromosome maintenance complex component 8	0.63	4.31E-05	0.58	5.40E-07
MLEC	malectin	0.73	4.72E-04	0.40	5.72E-27
MTSS1	metastasis suppressor 1	0.62	4.03E-06	0.50	1.40E-07
MVP	major vault protein	1.79	7.40E-06	1.71	4.42E-07
MYEOV	myeloma overexpressed	1.61	5.41E-06	7.91	9.68E-36
MYH9	myosin, heavy chain 9, non-muscle	1.40	1.61E-04	1.31	2.54E-04
MYO1B	myosin IB	1.86	7.24E-07	0.49	9.95E-09
NBPF1	neuroblastoma breakpoint family, member 1	0.67	1.65E-04	1.34	4.47E-04
NFKB2	nuclear factor of kappa light polypeptide gene enhancer in B-cells 2 (p49/p100)	1.51	2.64E-05	2.54	3.41E-18
NRP1	neuropilin 1	1.86	1.48E-06	0.66	6.22E-06
NTN4	netrin 4	2.39	1.18E-09	1.61	4.09E-06
NUAK2	NUAK family, SNF1-like kinase, 2	1.54	1.25E-04	3.70	2.45E-24
OAS1	2'-5'-oligoadenylate synthetase 1, 40/46kDa	4.56	1.67E-13	5.59	6.98E-40
OAS3	2'-5'-oligoadenylate synthetase 3, 100kDa	6.44	1.47E-14	1.46	2.86E-04
OPTN	optineurin	1.41	1.75E-04	3.34	3.27E-40
PANK1	pantothenate kinase 1	0.49	3.02E-08	0.41	8.97E-08
PAPOLA	poly(A) polymerase alpha	0.73	4.70E-04	0.64	2.32E-07
PARP14	poly (ADP-ribose) polymerase family, member 14	3.72	6.56E-13	0.67	1.88E-04
PBX2	pre-B-cell leukemia homeobox 2	1.50	3.61E-04	0.41	4.29E-17
PCYOX1	prenylcysteine oxidase 1	0.68	4.72E-05	0.53	8.08E-15
PHLDA3	pleckstrin homology-like domain, family A, member 3	1.61	4.30E-06	1.76	1.76E-05
PIK3R1	phosphoinositide-3-kinase, regulatory subunit 1 (alpha)	0.58	1.05E-06	0.55	2.55E-08
PIP4K2A	phosphatidylinositol-5-phosphate 4-kinase, type II, alpha	0.67	5.02E-05	1.69	9.73E-07
PKD1L2	polycystic kidney disease 1-like 2	1.44	6.25E-05	4.96	3.36E-20
PKIA	protein kinase (cAMP-dependent, catalytic) inhibitor alpha	0.68	4.88E-05	34.47	1.20E-07
PLXND1	plexin D1	0.74	4.50E-04	0.55	4.62E-13
PMP22	peripheral myelin protein 22	0.50	6.53E-08	4.20	2.83E-24
PODXL	podocalyxin-like	0.60	1.92E-06	4.33	2.82E-12
PROSER2	proline and serine rich 2	1.64	8.02E-06	2.96	4.68E-18
PSG4	pregnancy specific beta-1-glycoprotein 4	1.81	4.15E-07	8.37	4.03E-04

Supplementary Table 3. Common 252 genes regulated by NR2E3 deletion in both MCF-7 and HepG2 cells.

SYMBOL	Description	MCF-7		HepG2	
		Fold Change	P value	Fold Change	P value
PSME2	proteasome (prosome, macropain) activator subunit 2 (PA28 beta)	1.96	6.77E-06	0.63	3.26E-06
PTPN11	protein tyrosine phosphatase, non-receptor type 11	0.52	2.99E-07	0.36	7.79E-31
PVRL3	poliovirus receptor-related 3	0.57	3.33E-07	0.52	1.54E-05
PYGL	phosphorylase, glycogen, liver	1.43	3.21E-04	0.58	9.34E-10
PZP	pregnancy-zone protein	0.69	5.38E-05	0.26	3.79E-09
RAB11FIP3	RAB11 family interacting protein 3 (class II)	0.70	1.88E-04	0.62	6.77E-06
RAB22A	RAB22A, member RAS oncogene family	0.51	2.89E-08	1.39	4.36E-04
RAB29	RAB29, member RAS oncogene family	1.64	4.37E-06	1.81	1.14E-05
RAB4A	RAB4A, member RAS oncogene family	0.67	5.19E-05	0.46	2.98E-11
RAD51	RAD51 recombinase	0.72	3.91E-04	0.43	1.80E-04
RCC1	regulator of chromosome condensation 1	1.60	1.06E-05	0.61	1.54E-05
RIT1	Ras-like without CAAX 1	1.41	1.48E-04	4.21	1.57E-36
RNF213	ring finger protein 213	0.55	2.01E-06	0.75	2.43E-04
RRAS	related RAS viral (r-ras) oncogene homolog	2.03	2.62E-07	3.57	6.40E-14
S100A10	S100 calcium binding protein A10	2.70	1.70E-07	3.32	1.24E-42
S100A14	S100 calcium binding protein A14	1.51	1.65E-04	2.29	5.19E-07
SAT1	spermidine/spermine N1-acetyltransferase 1	1.56	1.39E-05	2.22	6.42E-10
SAYS1	SAYS1 motif domain containing 1	0.60	3.00E-06	0.37	8.19E-07
SEL1L3	sel-1 suppressor of lin-12-like 3 (C. elegans)	1.43	1.18E-04	2.83	2.41E-21
SERPINE2	serpin peptidase inhibitor, clade E (nexin, plasminogen activator inhibitor type 1), member 2	0.67	1.80E-05	1.40	2.19E-05
SFXN2	sideroflexin 2	0.58	7.60E-07	0.27	1.06E-06
SGK1	serum/glucocorticoid regulated kinase 1	0.53	4.56E-07	4.11	7.23E-28
SHCBP1	SHC SH2-domain binding protein 1	0.66	2.81E-05	0.17	5.26E-30
SLC25A15	solute carrier family 25 (mitochondrial carrier; ornithine transporter) member 15	0.68	4.32E-05	0.48	1.81E-08
SLC25A25	solute carrier family 25 (mitochondrial carrier; phosphate carrier), member 25	0.60	1.19E-06	2.37	1.92E-08
SLC38A1	solute carrier family 38, member 1	0.67	3.00E-04	1.52	3.89E-07
SLC47A1	solute carrier family 47 (multidrug and toxin extrusion), member 1	0.59	2.09E-05	0.31	3.34E-33
SLX1A	SLX1 structure-specific endonuclease subunit homolog A (S. cerevisiae)	1.40	4.14E-04	1.49	1.78E-05
SMARCB1	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily b, member 1	0.73	3.10E-04	0.66	1.80E-05
SNAPC1	small nuclear RNA activating complex, polypeptide 1, 43kDa	0.51	9.18E-08	1.97	9.08E-05
SNX10	sorting nexin 10	0.71	2.26E-04	0.68	3.49E-04
SP100	SP100 nuclear antigen	2.11	8.55E-08	1.50	9.41E-05
SP110	SP110 nuclear body protein	4.13	7.54E-13	2.10	2.95E-10
SPHAR	S-phase response (cyclin related)	0.68	5.57E-05	0.23	1.11E-04
SPINT1	serine peptidase inhibitor, Kunitz type 1	1.70	4.21E-05	4.24	3.60E-40
SPRY1	sprouty homolog 1, antagonist of FGF signaling (Drosophila)	1.54	2.88E-05	0.52	3.96E-05
STAT1	signal transducer and activator of transcription 1, 91kDa	4.88	4.48E-13	0.56	2.45E-10
STK19	serine/threonine kinase 19	1.41	3.65E-04	1.89	5.47E-06
STK40	serine/threonine kinase 40	1.40	4.52E-04	1.97	4.38E-14
STRA6	stimulated by retinoic acid 6	1.41	1.27E-04	0.13	4.60E-06
SYBU	syntabulin (syntaxin-interacting)	0.65	1.70E-05	2.97	3.11E-08
TAF9B	TAF9B RNA polymerase II, TATA box binding protein (TBP)-associated factor, 31kDa	0.69	1.85E-04	0.52	4.36E-05
TAGLN2	transgelin 2	1.44	1.78E-04	1.67	1.57E-08
TEX19	testis expressed 19	3.68	2.62E-12	14.96	1.37E-07
TGM2	transglutaminase 2	1.68	1.74E-06	1.87	1.35E-15
TIMP2	TIMP metalloproteinase inhibitor 2	1.55	1.80E-05	1.52	1.35E-07
TIPARP	TCDD-inducible poly(ADP-ribose) polymerase	0.64	3.92E-05	2.06	1.56E-08
TMEM140	transmembrane protein 140	1.76	1.77E-06	0.63	1.06E-04
TMEM181	transmembrane protein 181	0.64	2.67E-05	0.39	2.02E-27
TMEM241	transmembrane protein 241	0.71	3.56E-04	2.23	2.74E-05
TMEM254	transmembrane protein 254	0.55	1.00E-06	0.30	7.10E-08
TMSB4X	thymosin beta 4, X-linked	1.50	1.34E-04	2.21	6.16E-17
TNFRSF12A	tumor necrosis factor receptor superfamily, member 12A	2.16	5.28E-07	2.46	2.50E-21
TNFSF14	tumor necrosis factor (ligand) superfamily, member 14	0.56	6.97E-07	4.53	8.60E-12
TNFSF15	tumor necrosis factor (ligand) superfamily, member 15	0.62	4.81E-06	11.84	1.05E-18

Supplementary Table 3. Common 252 genes regulated by NR2E3 deletion in both MCF-7 and HepG2 cells.

SYMBOL	Description	MCF-7		HepG2	
		Fold Change	P value	Fold Change	P value
TNS3	tensin 3	1.62	3.98E-06	0.61	1.13E-08
TRAFD1	TRAF-type zinc finger domain containing 1	1.43	8.27E-05	1.62	4.41E-04
TRAK2	trafficking protein, kinesin binding 2	0.59	1.47E-06	1.48	1.48E-04
TRIB1	tribbles pseudokinase 1	0.65	7.35E-05	2.06	4.21E-16
TSC22D2	TSC22 domain family, member 2	1.46	5.25E-05	3.29	1.37E-25
TSPAN1	tetraspanin 1	1.61	2.00E-05	3.00	8.39E-27
TXNIP	thioredoxin interacting protein	1.73	1.71E-06	0.23	3.43E-20
UAP1L1	UDP-N-acetylglucosamine pyrophosphorylase 1 like 1	0.68	6.40E-05	1.91	4.76E-07
UBD	ubiquitin D	2.86	3.09E-10	0.32	1.31E-28
UBE2B	ubiquitin-conjugating enzyme E2B	0.68	8.86E-05	1.71	1.31E-06
UBE2Q1	ubiquitin-conjugating enzyme E2Q family member 1	0.63	1.96E-05	0.52	8.93E-06
UBE2Z	ubiquitin-conjugating enzyme E2Z	0.67	2.04E-05	0.66	1.10E-05
UHMK1	U2AF homology motif (UHM) kinase 1	0.66	3.91E-05	1.40	1.67E-04
UHRF1	ubiquitin-like with PHD and ring finger domains 1	0.70	2.16E-04	0.24	1.06E-23
VAV3	vav 3 guanine nucleotide exchange factor	0.69	1.50E-04	0.22	7.19E-10
WFS1	Wolfram syndrome 1 (wolframin)	0.65	1.20E-04	0.40	1.13E-08
WRAP53	WD repeat containing, antisense to TP53	0.69	1.56E-04	0.48	6.17E-07
XPO4	exportin 4	0.73	3.71E-04	0.48	6.22E-05
ZNF185	zinc finger protein 185 (LIM domain)	0.70	1.27E-04	3.07	5.98E-22
ZNF394	zinc finger protein 394	0.70	1.23E-04	1.93	2.52E-04
ZNF430	zinc finger protein 430	0.66	1.59E-05	2.65	1.90E-06
ZNF544	zinc finger protein 544	0.65	2.61E-05	0.42	9.19E-06
ZNFX1	zinc finger, NFX1-type containing 1	2.02	2.24E-08	1.89	1.84E-11

Supplementary Table. 4. Major signaling pathways associated with NR2E3 gene networks in HepG2 cells by Wikipathway analysis.

GeneSet Name	GeneSet ID	Enrichment Ratio	rawP	adjP Genes
Cell cycle	WP179	4.71	2.43E-20	1.24E-18
Adipogenesis	WP236	4.24	2.87E-19	9.76E-18
DNA Replication	WP466	7.24	9.77E-19	2.85E-17
G1 to S cell cycle control	WP45	4.68	1.67E-14	4.26E-13
Signaling Pathways in Glioblastoma	WP2261	4.42	4.59E-14	8.66E-13
Apoptosis	WP254	4.04	9.45E-13	1.61E-11
Complement and Coagulation Cascades	WP558	5.08	1.03E-11	1.24E-10
miRNA regulation of DNA Damage Response	WP1530	4.26	1.10E-11	1.25E-10
DNA damage response	WP707	4.28	2.22E-11	2.38E-10
Statin Pathway	WP430	5.63	7.00E-09	4.76E-08
Selenium Metabolism and Selenoproteins	WP28	4.37	1.38E-08	8.53E-08
IL-4 signaling pathway	WP395	4.01	1.46E-08	8.76E-08
Hypertrophy Model	WP516	6.19	2.11E-07	1.02E-06
Blood Clotting Cascade	WP272	5.2	6.98E-07	3.16E-06
G13 Signaling Pathway	WP524	4.26	1.58E-06	6.86E-06
SREBF and miR33 in cholesterol and lipid homeostasis	WP2011	6.33	2.19E-06	9.31E-06
AhR pathway	WP2100	4.04	3.29E-06	1.37E-05
Complement Activation, Classical Pathway	WP545	5.96	4.28E-06	1.71E-05
Mismatch repair	WP531	6.43	7.08E-06	2.78E-05
ID signaling pathway	WP53	6	1.40E-05	4.76E-05
Triacylglyceride Synthesis	WP325	4.69	1.84E-05	6.15E-05
Fatty Acid Biosynthesis	WP357	4.27	2.04E-05	6.61E-05
Nucleotide Metabolism	WP404	5.07	2.31E-05	7.36E-05
Glutathione metabolism	WP100	4.5	2.83E-05	8.62E-05
Oxidative Stress	WP408	4.13	2.96E-05	8.84E-05
Adipocyte TarBase	WP2001	4.61	5.80E-05	0.0002
TCA Cycle	WP78	4.5	0.0002	0.0005
IL-7 signaling pathway	WP205	4.05	0.0002	0.0005
Keap1-Nrf2 Pathway	WP3	4.64	0.0004	0.0009
Urea cycle and metabolism of amino groups	WP497	4.09	0.0004	0.0009
TP53 network	WP1742	4.15	0.0008	0.0016
Benzo(a)pyrene metabolism	WP696	5.12	0.0016	0.003
Glial Cell Differentiation	WP2276	6.43	0.0017	0.0031
E2F-MIRHG1 feedback-loop	WP1537	8.44	0.0026	0.0047
Glycoprotein VI platelet signaling	WP1970	11.26	0.0079	0.0128
Nifedipine Activity	WP259	5.63	0.0114	0.018
IL12 SIGNALING PATHWAY	WP2111	4.09	0.0123	0.0192
Integrated Cancer pathway	WP1971	7.5	0.0223	0.0335
Methylation Pathways	WP704	4.22	0.0279	0.0398
Pentose Phosphate Pathway	WP134	4.22	0.0279	0.0398

Supplementary Table. 5. Major signaling pathways associated with NR2E3 gene networks in MCF-7 cells by WikiPathway analysis .

GeneSet Name	GeneSet ID	Enrichment Ratio	rawP	adjP
B Cell Receptor Signaling Pathway	WP23	6.13	0.0043	0.0091
TWEAK Signaling Pathway	WP2036	9.35	0.0041	0.0089
Alpha 6 Beta 4 signaling pathway	WP244	10.48	0.003	0.0067
Type III interferon signaling	WP2113	24.94	0.0028	0.0064
Insulin Signaling	WP481	5.36	0.0026	0.0061
Leukocyte TarBase	WP2003	5.46	0.0024	0.0058
Regulation of toll-like receptor signaling pathway	WP1449	5.67	0.002	0.005
AhR pathway	WP2100	13.43	0.0015	0.0039
Oncostatin M Signaling Pathway	WP2358	8.22	0.0015	0.0039
IL17 signaling pathway	WP2112	13.78	0.0014	0.0038
Leptin signaling pathway	WP2034	8.62	0.0012	0.0034
Methylation Pathways	WP704	43.65	0.0009	0.0026
miRNA regulation of DNA Damage Response	WP1530	9.44	0.0009	0.0026
DNA damage response	WP707	9.84	0.0008	0.0025
Oxidative Stress	WP408	17.46	0.0007	0.0023
metapathway biotransformation	WP702	5.92	0.0006	0.002
TCR Signaling Pathway	WP69	8.24	0.0004	0.0014
Cell cycle	WP179	7.94	0.0004	0.0014
IL-3 Signaling Pathway	WP286	12.93	0.0003	0.0012
IL-6 signaling pathway	WP364	12.04	0.0003	0.0012
angiogenesis overview	WP1993	11.05	9.44E-05	0.0008
Signaling Pathways in Glioblastoma	WP2261	10.39	0.0001	0.0008
Adipogenesis	WP236	8.06	0.0001	0.0008
IL-5 signaling pathway	WP127	14.86	0.0002	0.0008
Interleukin-11 Signaling Pathway	WP2332	14.25	0.0002	0.0008
TSLP Signaling Pathway	WP2203	14.25	0.0002	0.0008
IL-2 Signaling pathway	WP49	13.18	0.0002	0.0008
Prolactin Signaling Pathway	WP2037	9.49	0.0002	0.0008
Apoptosis	WP254	9.49	0.0002	0.0008
Squamous cell TarBase	WP2006	6.98	0.0002	0.0008
Epithelium TarBase	WP2002	4.62	0.0002	0.0008
Muscle cell TarBase	WP2005	4.12	0.0002	0.0008
EGF-EGFR Signaling Pathway	WP437	7.11	6.50E-05	0.0007
Lymphocyte TarBase	WP2004	3.93	6.71E-05	0.0007
Senescence and Autophagy	WP615	8.73	7.04E-05	0.0007
IL-4 signaling pathway	WP395	14.8	2.30E-05	0.0005
Prostaglandin Synthesis and Regulation	WP98	22.53	2.93E-05	0.0005
Type II interferon signaling (IFNG)	WP619	13.26	6.51E-06	0.0002
Interferon type I	WP585	16.37	1.89E-06	9.61E-05
Kit receptor signaling pathway	WP304	15.87	2.26E-06	9.61E-05

Supplementary Table 6. Expression levels of NR2E3 in normal human liver tissue.

Sample #	Diagnosis	NR2E3 staining Intensity
1	Normal	40
2	Normal	100
3	Normal	100
4	Normal	100
5	Normal	100
6	Normal	60
7	Normal	100
8	Normal	100
9	Normal	100

Supplementary Table. 7. Expression levels of NR2E3 in cirrhotic human liver tissues.

Sample #	Diagnosis	Associated lesion	NR2E3 staining Intensity
1	macronodular cirrhosis	Hepatocellular carcinoma	100
2	macronodular cirrhosis	Hepatocellular carcinoma	100
3	macronodular cirrhosis	Hepatocellular carcinoma	100
4	macronodular cirrhosis	Hepatocellular carcinoma	100
5	macronodular cirrhosis	Hepatocellular carcinoma	100
6	macronodular cirrhosis	Hepatocellular carcinoma	100
7	macronodular cirrhosis	Hepatocellular carcinoma	100
8	macronodular cirrhosis	Hepatocellular carcinoma	100
9	macronodular cirrhosis	Hepatocellular carcinoma	100
10	macro- and micronodular cirrhosis	Hepatocellular carcinoma	100
11	macronodular cirrhosis	Hepatocellular carcinoma	80
12	macronodular cirrhosis	Hepatocellular carcinoma	80
13	macro- and micronodular cirrhosis	Hepatocellular carcinoma	80
14	macronodular cirrhosis	Hepatocellular carcinoma	70
15	macronodular cirrhosis	Hepatocellular carcinoma	60
16	macronodular cirrhosis	Hepatocellular carcinoma	60
17	macronodular cirrhosis	Hepatocellular carcinoma	60
18	macronodular cirrhosis	Hepatocellular carcinoma	60
19	macro- and micronodular cirrhosis	Hepatocellular carcinoma	60
20	macro- and micronodular cirrhosis	Hepatocellular carcinoma	60
21	macronodular cirrhosis	Hepatocellular carcinoma	50
22	macronodular cirrhosis	Hepatocellular carcinoma	50
23	macronodular cirrhosis	Hepatocellular carcinoma	30
24	macro- and micronodular cirrhosis	Hepatocellular carcinoma	30

Supplementary Table 8. Clinical information and expression levels of NR2E3 in human liver tumor tissue samples (Hepatocellular carcinoma, HCC).

Sample #	Diagnosis	T stage	N stage	M stage	NR2E3 staining Intensity (%)
1	HCC	T1	N0	M0	100
2	HCC	T1	N0	M0	10
3	HCC	T1	N0	M0	100
4	HCC	T1	N0	M0	0
5	HCC	T1	N0	M0	70
6	HCC	T1	N0	M0	10
7	HCC	T1	N0	M0	15
8	HCC	T1	N0	M0	10
9	HCC	T1	N0	M0	0
10	HCC	T1	N0	M0	50
11	HCC	T1	N0	M0	0
12	HCC	T1	N0	M0	15
13	HCC	T1	N0	M0	20
14	HCC	T1	N1	M0	100
15	HCC	T2	N0	M0	100
16	HCC	T2	N0	M0	40
17	HCC	T2	N0	M0	0
18	HCC	T2	N0	M0	20
19	HCC	T2	N0	M0	100
20	HCC	T2	N0	M0	100
21	HCC	T2	N0	M0	0
22	HCC	T2	N0	M0	100
23	HCC	T2	N0	M0	100
24	HCC	T2	N0	M1	10
25	HCC	T2	Nx	M0	100
26	HCC	T3	N0	M0	0
27	HCC	T3	N0	M0	20
28	HCC	T3	N0	M0	10
29	HCC	T3	N0	M0	60
30	HCC	T3	N0	M0	40
31	HCC	T3	N0	M0	100
32	HCC	T3a	N0	M0	0
33	HCC	T3a	N0	M0	0
34	HCC	T3a	N0	M0	0
35	HCC	T3a	N0	M0	100
36	HCC	T3a	N0	M0	0
37	HCC	T4	Nx	M1	100
38	HCC	T4	N0	M0	40
39	HCC	T4	N0	M0	40
40	HCC	T4	N1	M0	0
41	HCC	TM	Nx	M1	60
42	HCC	TM	Nx	M1	80
43	HCC	TM	Nx	M1	20
44	HCC	TM	Nx	M1	10
45	HCC	TM	Nx	M1	100
46	HCC	TM	N0	M1	20
47	HCC	TM	N1	M0	70
48	HCC	TM	Nx	M1	0
49	HCC		N1	M0	100
50	HCC				100

Figure 3

Fig. 3b

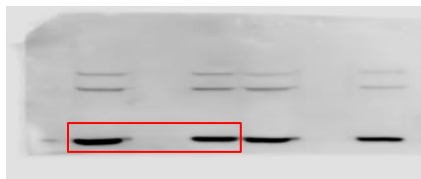


Fig. 3d

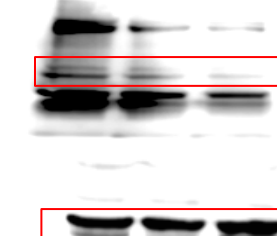
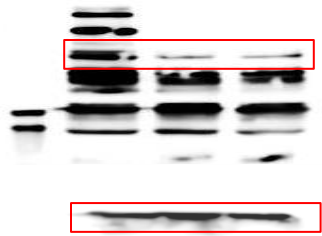
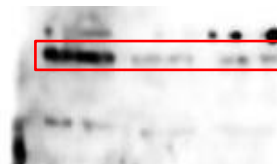
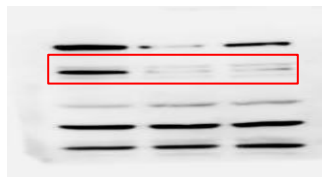


Figure 4

Fig. 4a

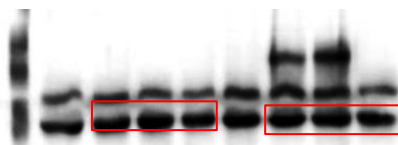
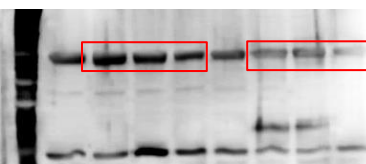
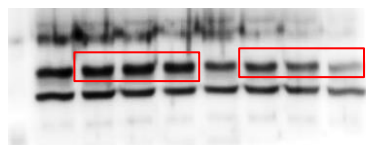


Figure 5

Fig. 5a

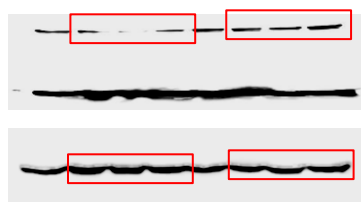
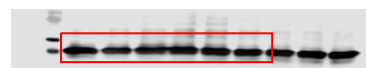
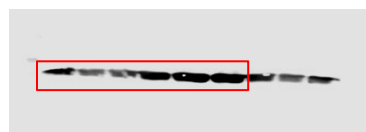


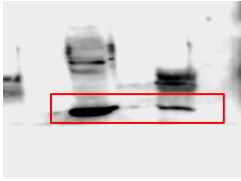
Fig. 5f



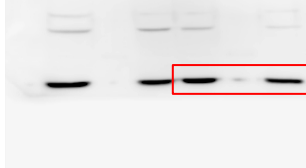
Supplementary Fig. 10 Uncropped gels and western blots. The red boxes indicate the cropped regions.

Supplementary Figure 1.

Sup.Fig. 1a

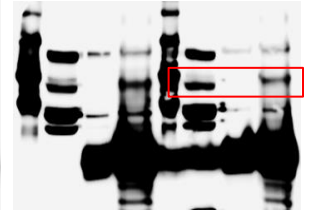
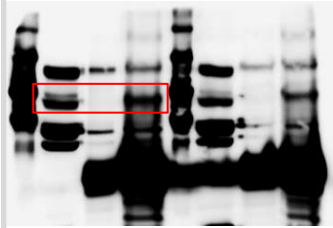


Sup.Fig. 1b



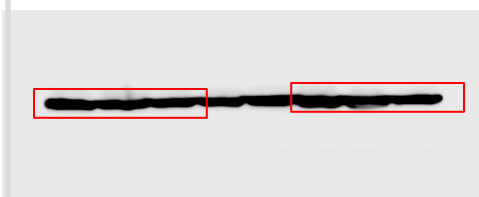
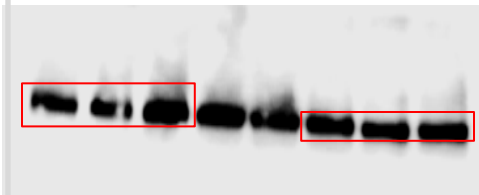
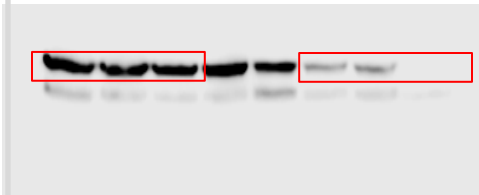
Supplementary Figure 2.

Sup.Fig. 2a



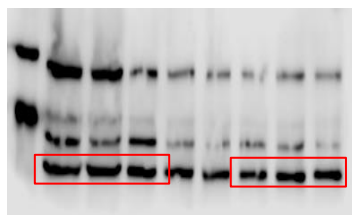
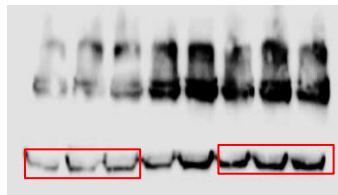
Supplementary Figure 3.

Sup.Fig. 3b



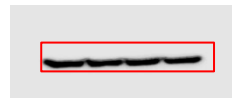
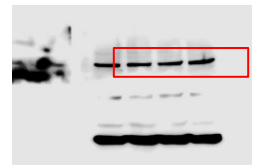
Supplementary Figure 6.

Sup.Fig. 6a



Supplementary Figure 7.

Sup.Fig. 7a



Supplementary Fig. 11 Uncropped gels and western blots. The red boxes indicate the cropped regions