

SUPPLEMENTARY INFORMATION

Basal expression of interferon regulatory factor 1 drives intrinsic hepatocyte resistance to multiple RNA viruses

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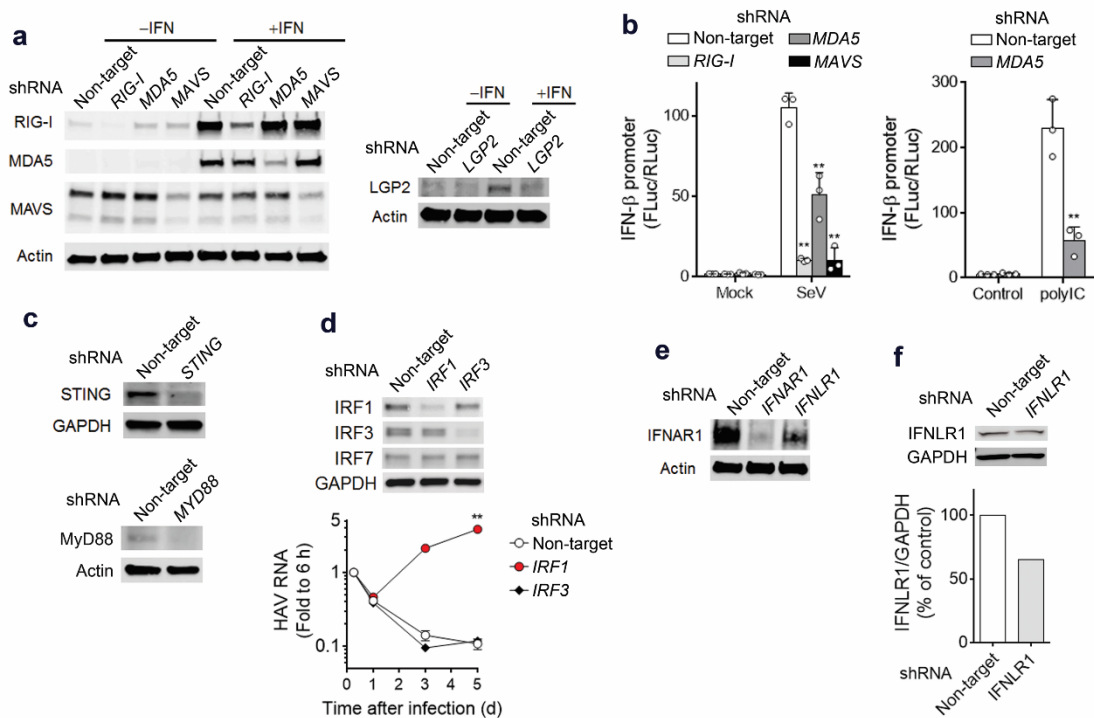
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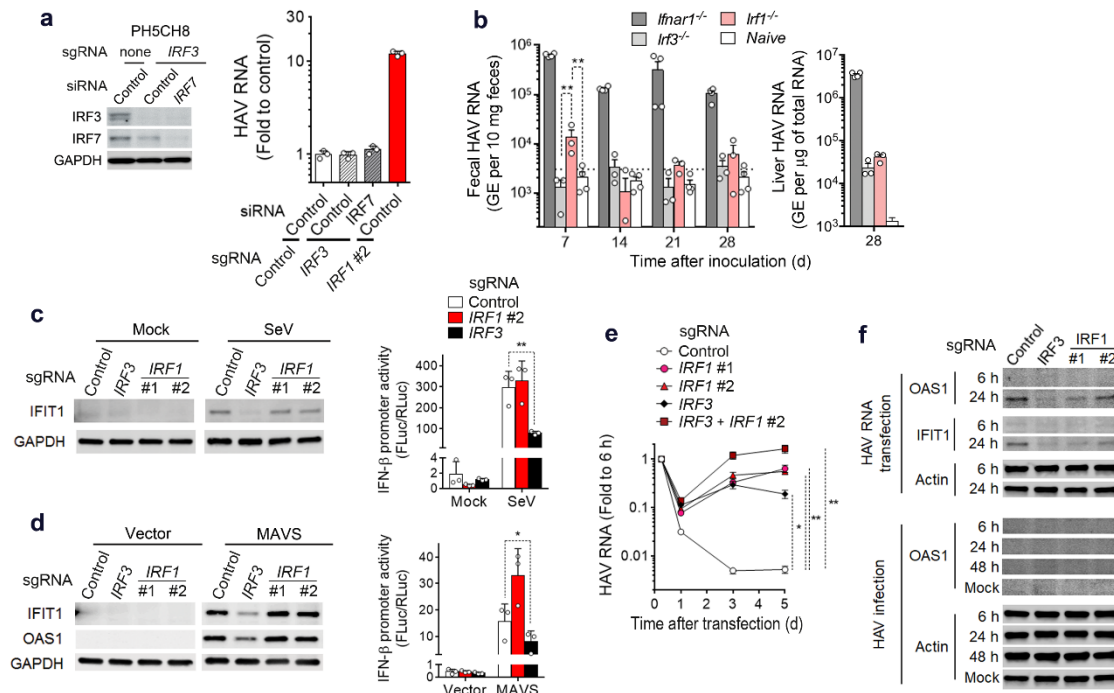
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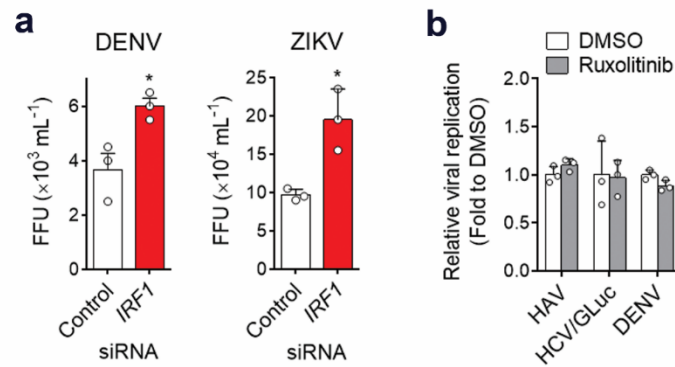
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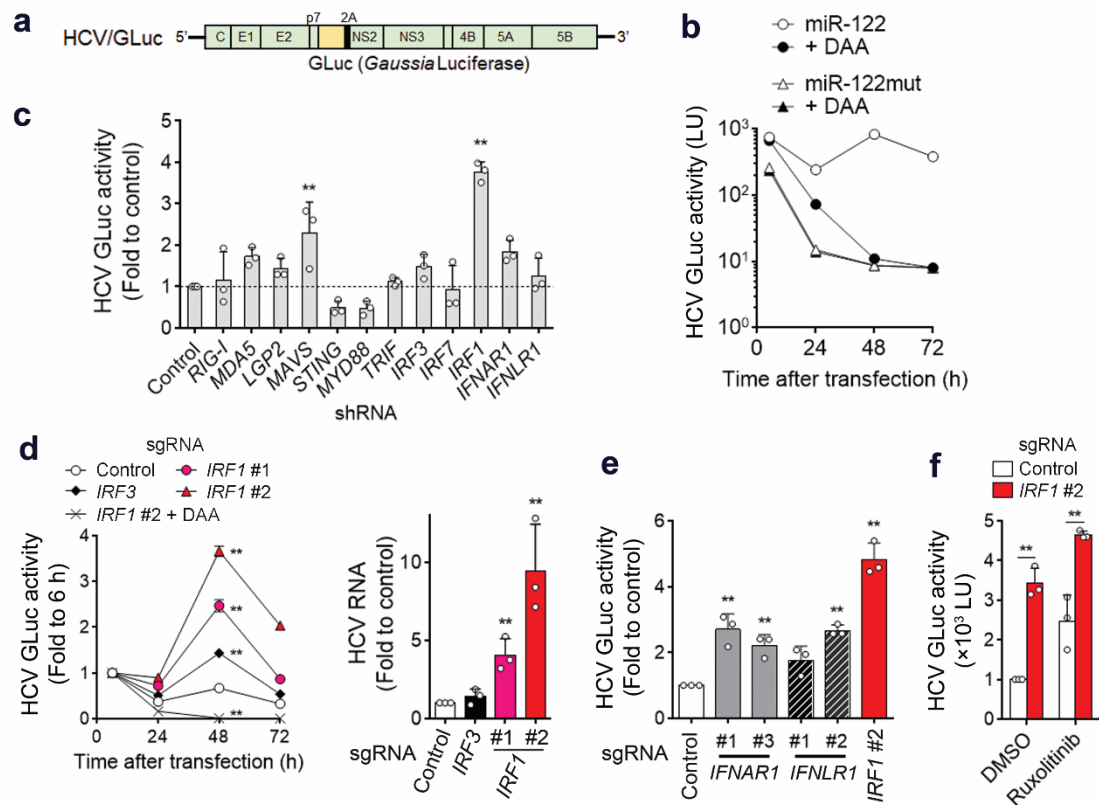
Supplementary Figure 1. shRNA-mediated knockdown of host factors linked to RLR and TLR signaling pathways. (a) Immunoblots of RIG-I-like receptors (RLRs) in PH5CH8 cells stably expressing indicated shRNAs. Cells were stimulated with 100 U ml^{-1} IFN- α for 24 h where indicated. (b) Functional depletion of the RLRs was confirmed by stimulation with either Sendai virus (SeV) challenge (50 U ml^{-1}) or polyIC transfection ($1 \mu\text{g ml}^{-1}$). Values shown are mean \pm s.d. from 3 independent experiments. $**p < 0.0001$ vs. non-targeting control (two-way ANOVA with Sidak's multiple comparisons test). (c) Immunoblots of STING and MyD88 in the indicated shRNA-transduced PH5CH8 cells. (d) shRNA knockdown of *IRF1* and *IRF3* and its effects on HAV replication over ensuing 5 days. Values shown are mean \pm s.d. of 3 technical replicates representative of 2 independent experiments. $*p < 0.0001$ vs. non-target shRNA, by two-way ANOVA with Dunnett's multiple comparisons test. (e) Immunoblot of IFNAR1 in PH5CH8 cells transfected with shRNA targeting *IFNAR1* versus *IFNLR1*. (f) Immunoblot of IFNLR1 in PH5CH8 cells expressing shRNA targeting *IFNLR1*. Normalized quantity of IFNLR1 is shown below. Data shown in (a, c, e, f) are representative of 2 independent experiments.



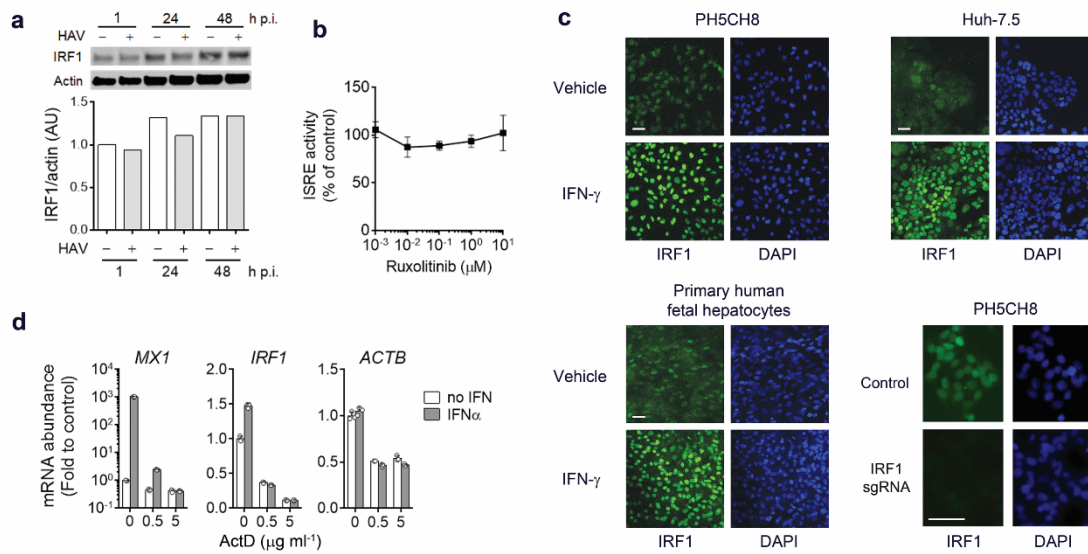
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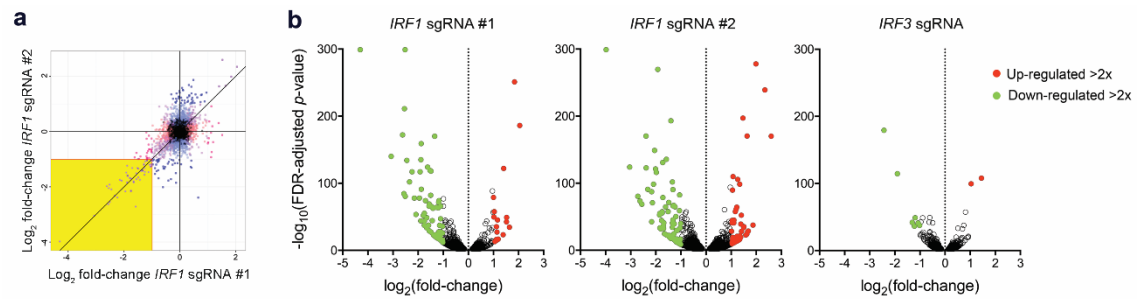
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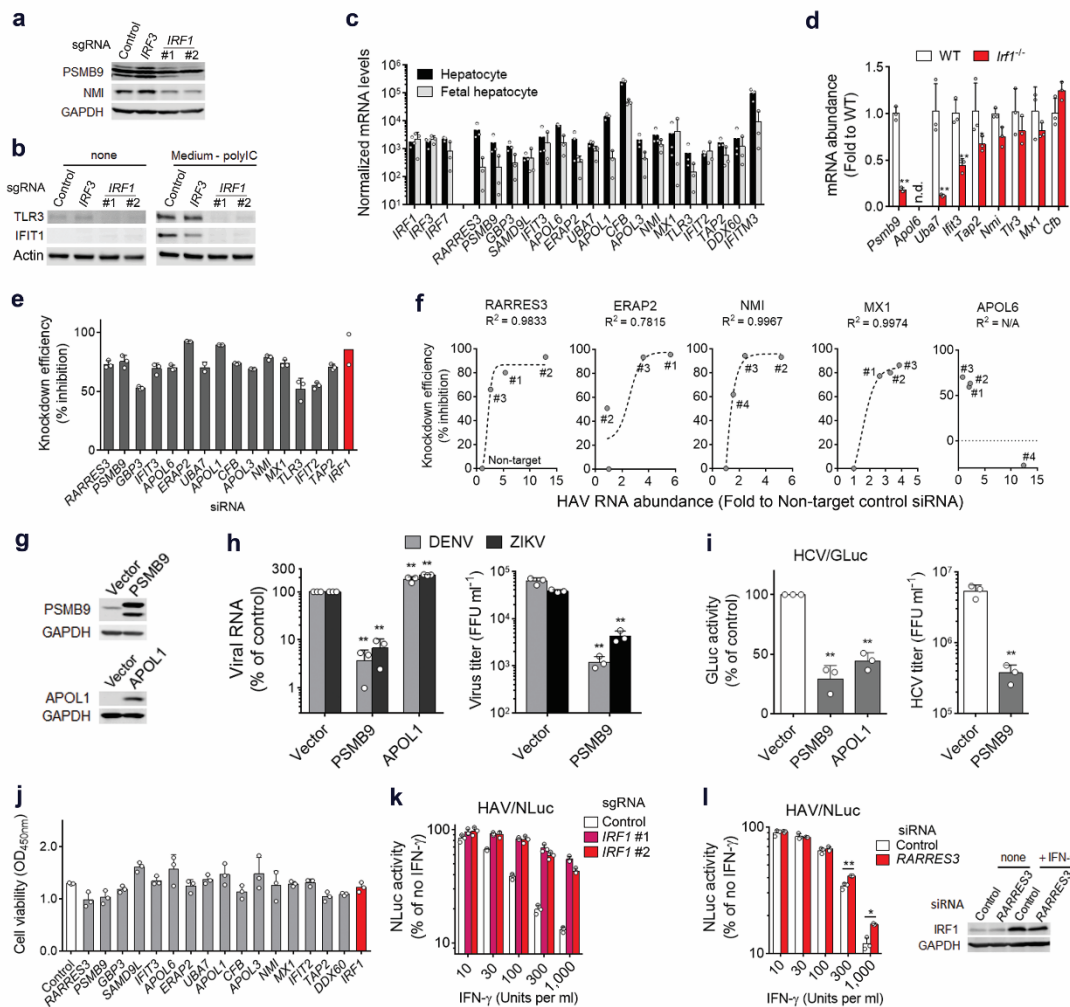
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Supplementary Figure 5. Regulation of basal and induced IRF1 abundance and IRF1 transcriptional activity. (a) IRF1 protein abundance is not altered following HAV challenge of PH5CH8 cells at an m.o.i. of 10. Relative IRF1 protein abundance normalized to that of actin is shown below. Data shown are representative of 2 independent experiments. (b) Basal ISRE activity in PH5CH8 cells is not regulated by JAK/STAT signaling. PH5CH8 cells were treated with indicated doses of ruxolitinib and ISRE promoter activity measured. Values shown are mean \pm s.e.m. from 3 technical replicates representative of 2 independent experiments. (c) Nuclear localization of IRF1 in different hepatic cell cultures under basal conditions and following treatment with the agonist IFN- γ (1,000 U ml $^{-1}$ for 24 h). The antibody staining of PH5CH8 cells expressing control vs. IRF1 #1 sgRNAs is shown on lower right panels to demonstrate the specificity of the nuclear IRF1 signals. Scale bar, 50 μm . Data shown are representative of 2 independent experiments. (d) Inhibition of *de novo* transcription of cellular genes following treatment with different concentrations of actinomycin D (ActD). Huh-7.5 cells pretreated with ActD were stimulated with 100 U ml $^{-1}$ IFN α for 16 h and analyzed for transcripts of two IFN-responsive genes (*MX1* and *IRF1*) and actin (*ACTB*). Values shown are mean \pm s.d. from 3 technical replicates.

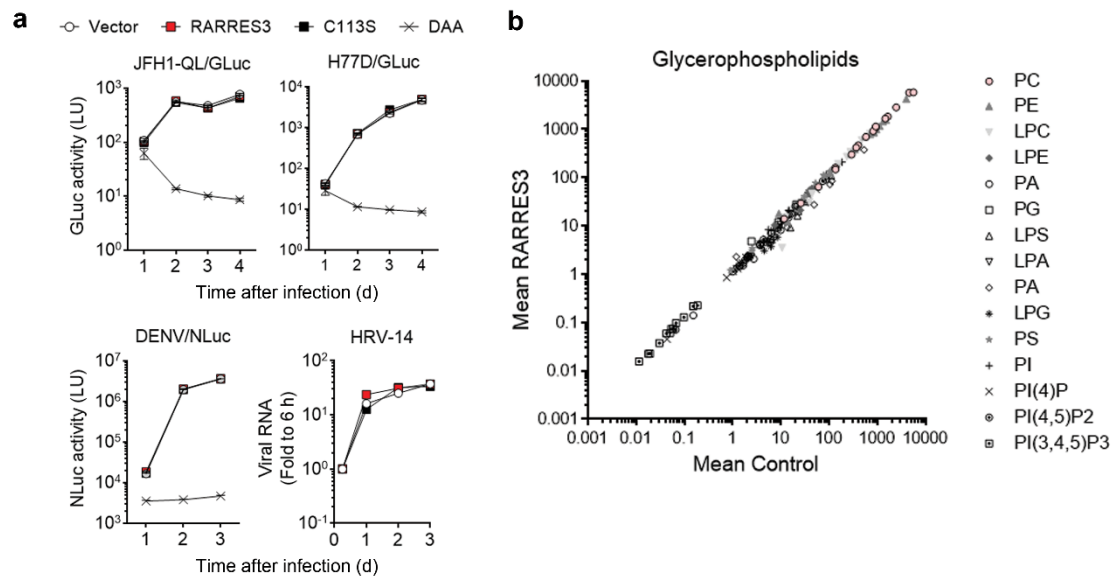


Supplementary Figure 6. Transcriptomic analysis of PH5CH8 cells expressing *IRF1* vs. *IRF3* sgRNAs. RNA samples extracted from HAV-infected PH5CH8 cells expressing *IRF1* #1, *IRF1* #2, *IRF3*, and control sgRNAs in triplicate cultures were subjected to high throughput sequencing. Reads were identified from an average of $16,402 \pm 151$ s.d. genes in each cell line. Compared with control cells, 652 genes were down-regulated (adjusted p-value < 0.01) in *IRF1* sgRNA #1 cells, 71 of which were down-regulated >2 -fold, whereas 1100 genes were down-regulated in *IRF1* sgRNA #2 cells (89 >2 -fold); 559 genes were up-regulated in *IRF1* sgRNA #1 cells (17 >2 -fold), and 871 genes in *IRF1* sgRNA #2 cells (48 >2 -fold). In aggregate, 48 genes were downregulated and 4 upregulated >2 -fold in both *IRF1* sgRNA expressing cell lines, and not similarly regulated in *IRF3* sgRNA cells. (a) Scatter plots showing changes in relative transcript levels of genes in PH5CH8 cell lines expressing the two independent *IRF1* sgRNAs. Each symbol represents mean value of RNA transcript reads from 3 technical replicates. Note that genes reduced >2 -fold are highly congruent (highlighted in the yellow area). (b) Volcano plots showing changes in relative RNA transcript abundance in the PH5CH8 cell lines expressing indicated sgRNAs. Each symbol represents mean value of RNA transcript reads from 3 technical replicates. The p-values were determined using the negative binomial Wald test. The p-values were adjusted using false discovery rate (FDR) correction.



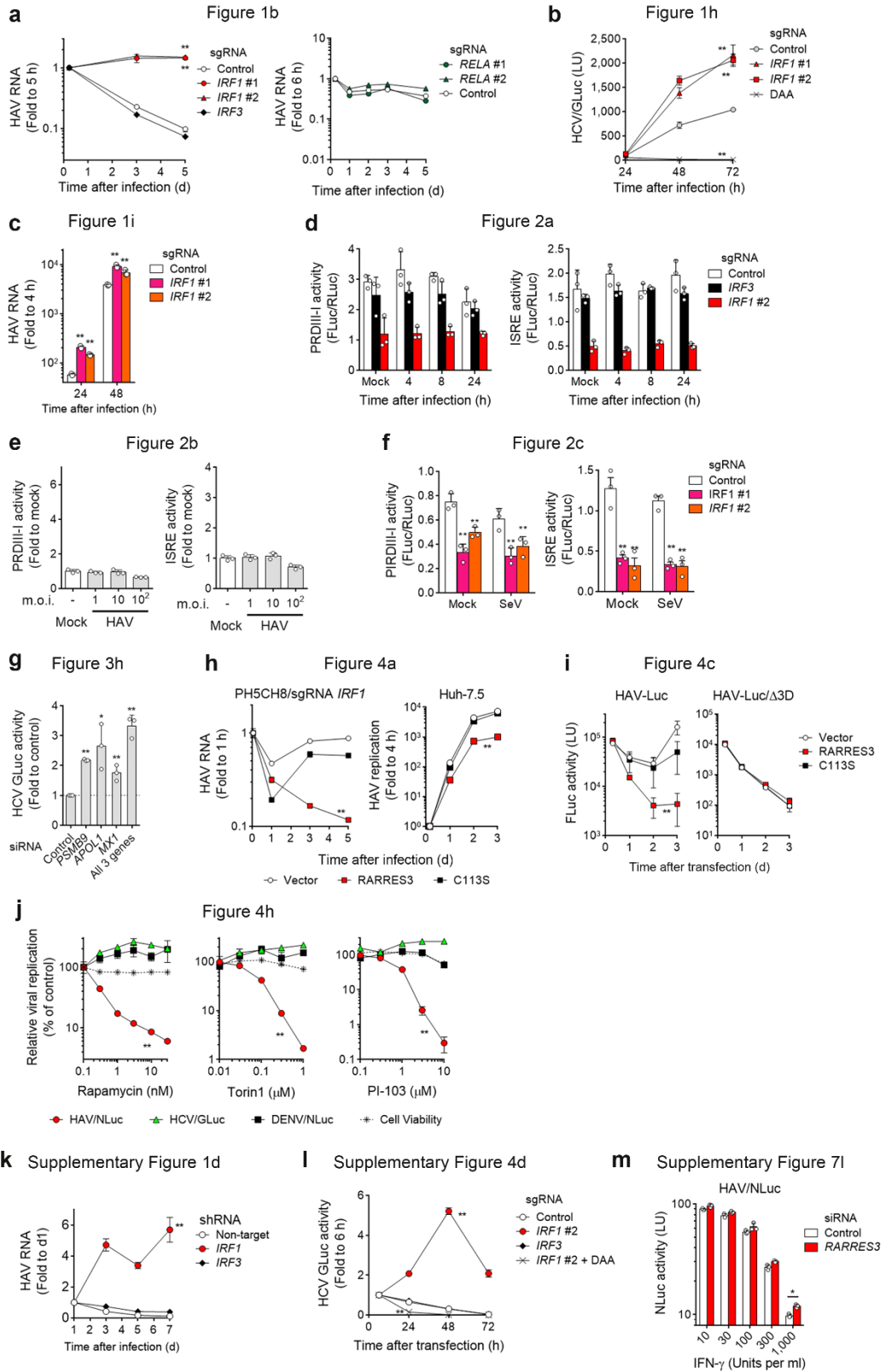
Supplementary Figure 7. Antiviral activities of IRF1 target genes and their IRF1-dependent expression *in vitro* and *in vivo*. (a) The basal protein expression of IRF1-regulated genes, PSMB9 and NMI, is reduced in PH5CH8 cells expressing *IRF1* sgRNAs. Data shown are representative of 2 independent experiments. (b) Both basal expression of TLR3 and TLR3-mediated induction of the ISG, IFIT1, in response to poly(I:C) added to culture medium (50 $\mu\text{g ml}^{-1}$ for 6 h) are impaired in *IRF1* sgRNA-expressing PH5CH8 cells. Data shown are representative of 2 independent experiments. (c) Abundance of basally-expressed *IRF1*, *IRF3*, *IRF7* and IRF1-responsive gene transcripts in primary adult human hepatocytes and human fetal hepatocytes. Values shown are means \pm s.d. from 3 independent donors and are from previously published data¹⁹. (d) Basal expression levels of select IRF1 target gene mRNAs are reduced in *Ifit1*^{-/-} mouse liver tissues. Values shown are mean \pm s.d. of 3 animals. n.d., not detected. ** $p < 0.0001$ (*Psmb9*, *Uba7*), $p = 0.0002$ (*Ifit3*), vs. WT (two-sided unpaired t-test). (e) Knockdown efficiency of IRF1 effector genes as assessed by quantitative RT-PCR or by immunoblot analysis for IRF1 protein shown in red. Values shown are means \pm s.d. from 3 technical replicates (RNA abundance) or from 2 biological replicates (IRF1 protein abundance). (f) Correlation between knockdown efficiency of individual siRNAs (Y-axis) versus replication enhancement of HAV RNA (X-axis). Each symbol represents a mean value from a single siRNA, each analyzed in 3 technical replicates. Nonlinear regression curves were fit according to a three-parameter model. (g) Immunoblots of PSMB9 and APOL1 expressed in Huh-7.5 cells stably transduced with indicated lentiviral vectors. Data shown are representative of two independent experiments. (h) Replication of flavivirus RNA and infectious virus titers at 24 h p.i. in Huh-7.5 cells expressing the indicated

genes. Values shown are means \pm s.d. from 3 independent experiments. $**p < 0.0001$ vs. vector control (two-way ANOVA with Sidak's multiple comparisons test) (i) GLuc activities reflecting replication of JFH1-QL/GLuc virus on 3 d p.i. (left) and infectious titers of JFH1-QL virus on 3 day post RNA transfection (right) in Huh-7.5 cells expressing the indicated genes. Values shown are means \pm s.d. from 3 independent experiments. $**p = 0.0002$ (GLuc, PSMB9), $p = 0.0004$ (GLuc, APOL1), $p = 0.0016$ (virus titer) vs. control (two-sided unpaired t-test) (j) Cell viability in Huh-7.5 cells transfected with indicated siRNAs directed to *IRF1* and its target genes as measured by WST-8 assay. Values shown are means \pm s.d. from 3 technical replicates. (k) IFN- γ , an IRF1-agonist, restricts HAV replication via an IRF1-dependent mechanism. Note that the anti-HAV action of IFN- γ is diminished in Huh-7.5 cell lines expressing two independent *IRF1* sgRNAs. Values shown are means \pm s.d. from 3 technical replicates and are representative of 2 independent experiments. (l) Depletion of RARRES3 partially attenuates the anti-HAV effect of overexpressed IRF1. Immunoblots of IRF1 and GAPDH are shown on right (IFN- γ , 1,000 U ml $^{-1}$ for 24 h). Values shown are means \pm s.d. from 3 technical replicates and are representative of 3 independent experiments. $*p = 0.0309$, $**p = 0.005$ vs. control (two-way ANOVA with Dunnett's multiple comparisons test).



Supplementary Figure 8. Effect of RARRES3 overexpression on replication of HCV, DENV and HRV-14, and cellular glycerophospholipid profiles in Huh-7.5 cells. (a) Replication of HCV/GLuc (genotype 2a JFH1-QL and genotype 1a H77D), DENV/NLuc, or human rhinovirus 14 (HRV-14) in Huh-7.5 cells stably expressing empty vector, RARRES3, or RARRES3/C113S (catalytically inactive). DAA, sofosbuvir for HCV/GLuc or 2'CMA for DENV/NLuc (30 μ M each). Values shown are mean \pm s.d. from 3 technical replicates. (b) Glycerophospholipid profiles of Huh-7.5 cells stably expressing RARRES3 vs. empty vector control. Units are pmol per 10^6 cells. Values shown are mean \pm s.d. from 3 independent experiments.

Supplementary Figure 9. Data for additional biological replicates. (a-m) Number of experimental replicates and statistical tests are equivalent to that of the main figures.



Supplementary Figure 10. Uncropped blots.

Boxes indicate the cropped areas shown in the indicated figures. Molecular weight is indicated in numbers.

Figure 1b

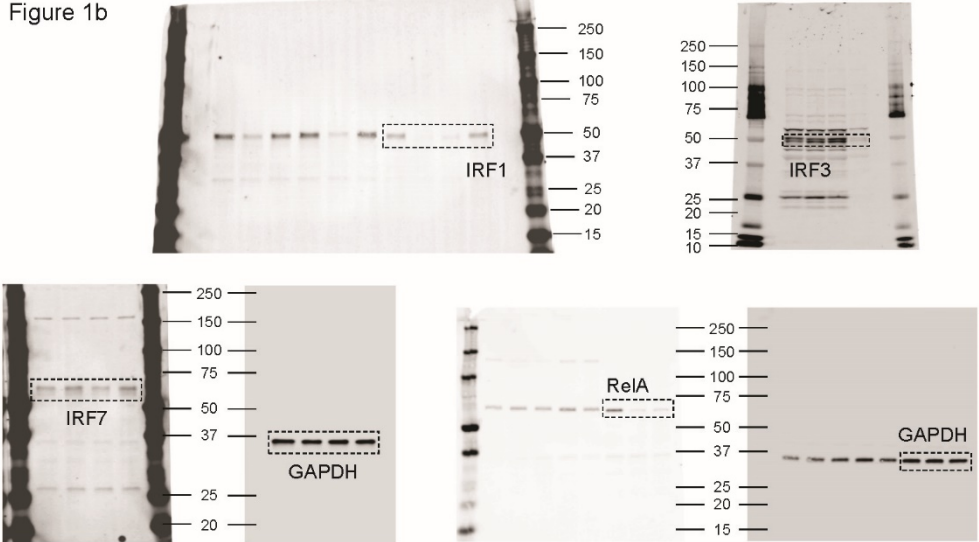


Figure 1d

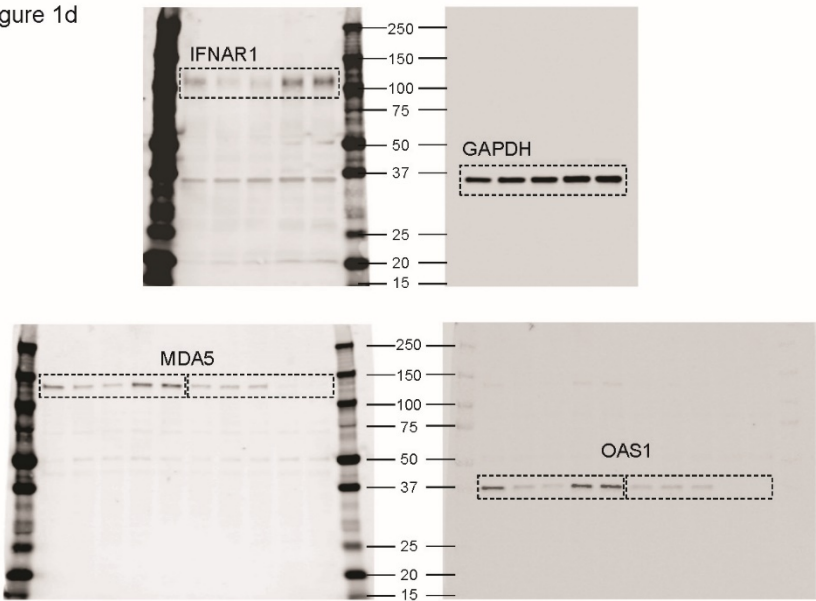


Figure 1e

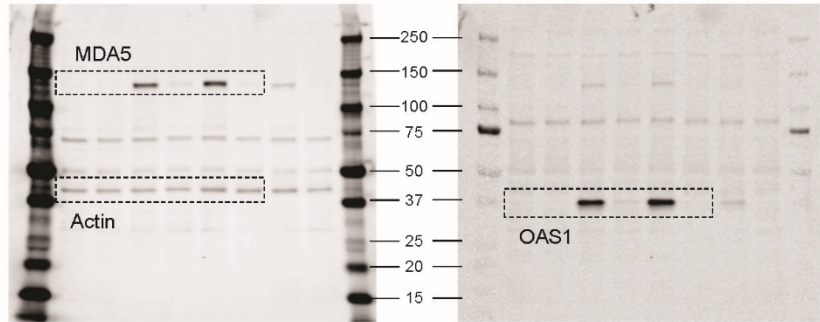


Figure 1g

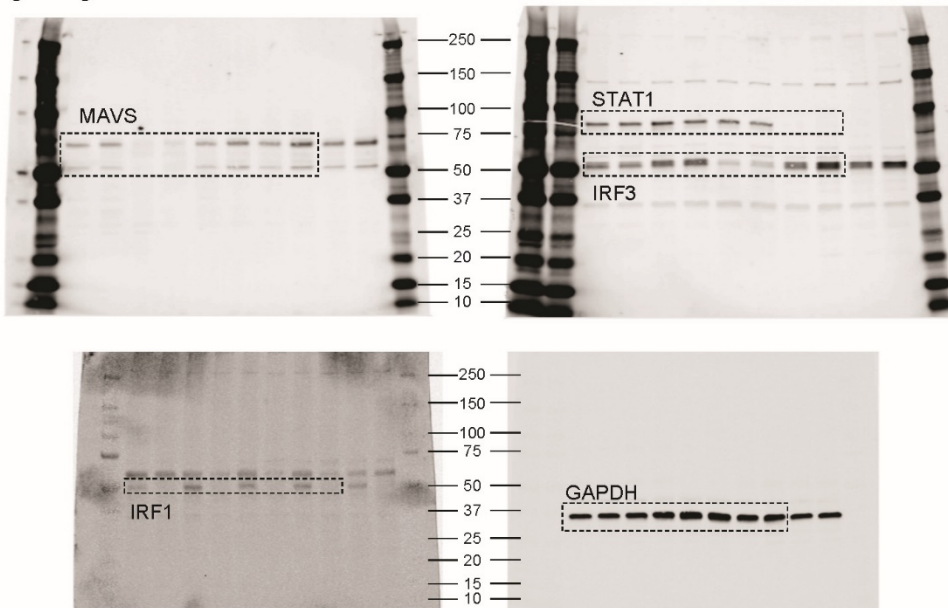


Figure 1h

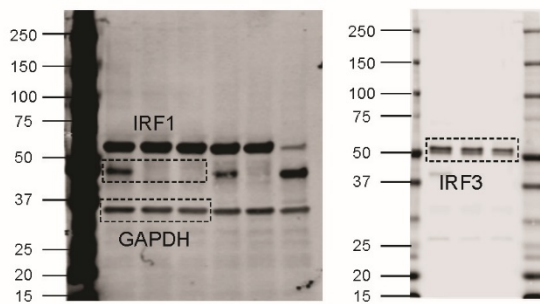


Figure 4a

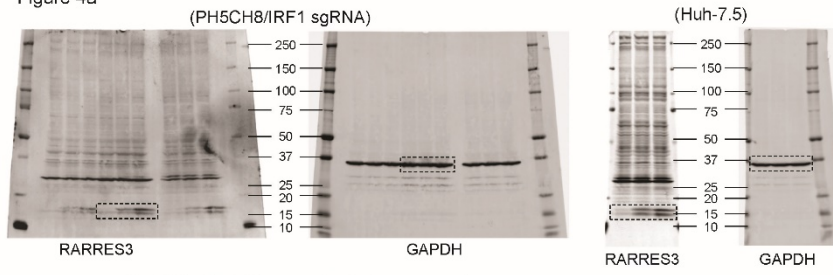


Figure 4d

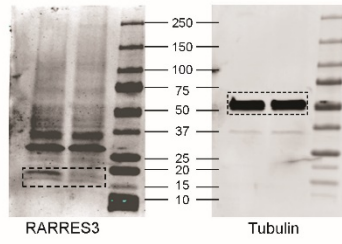


Figure 4e

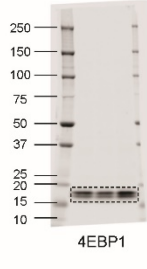
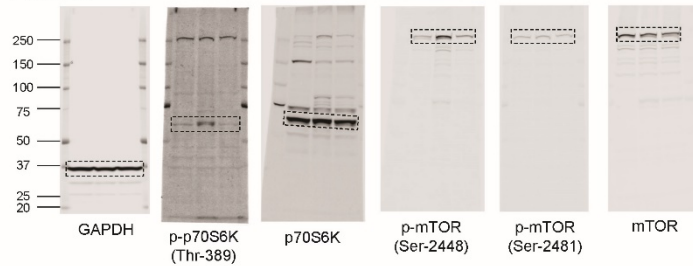


Figure 4f

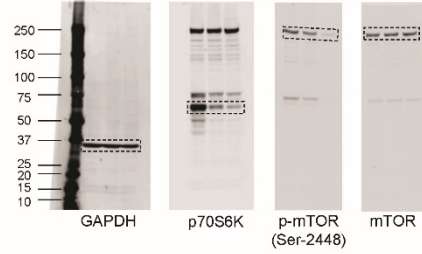
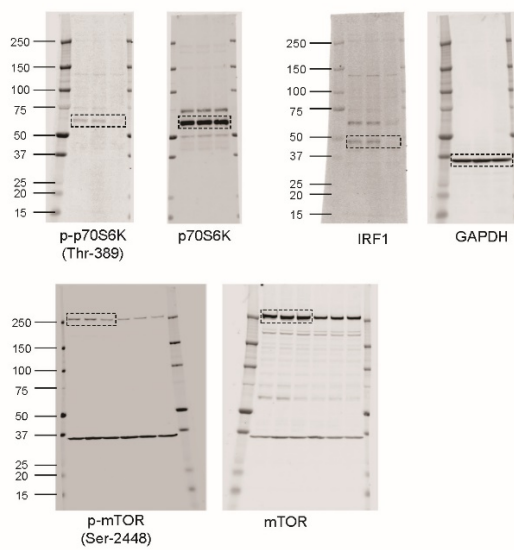
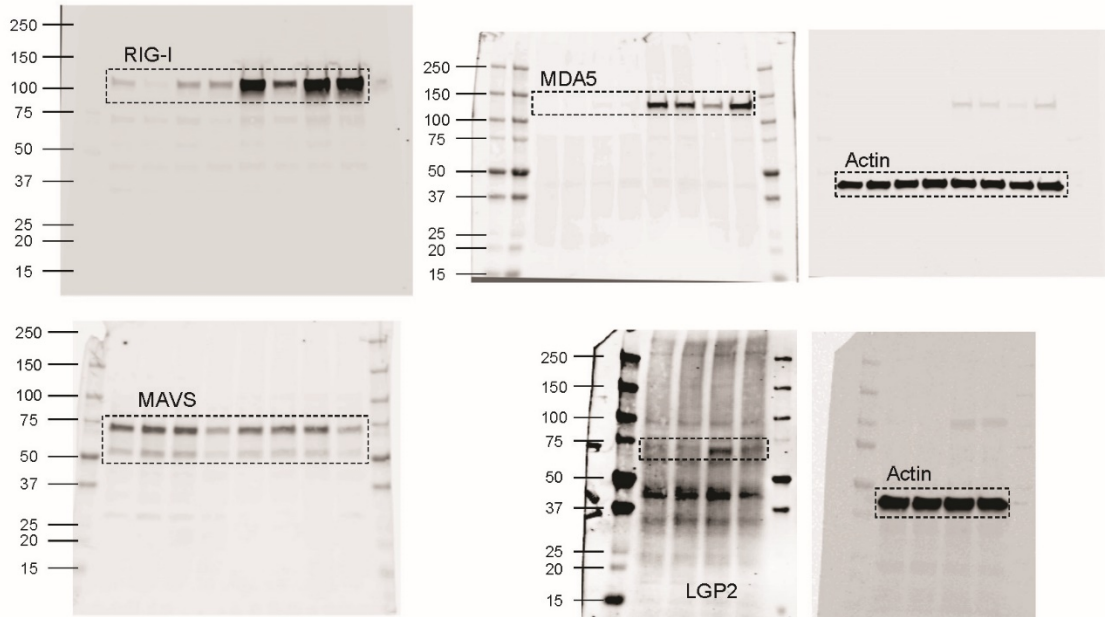


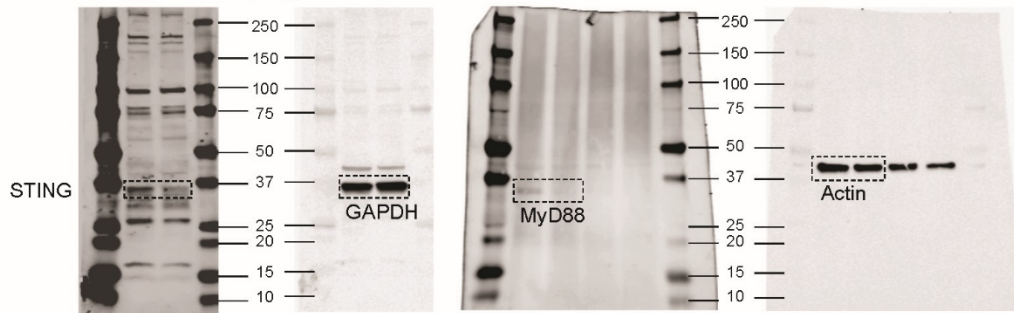
Figure 4g



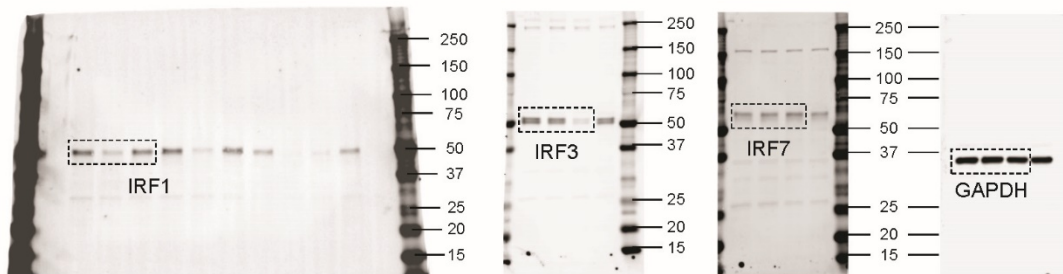
Supplementary Figure 1a



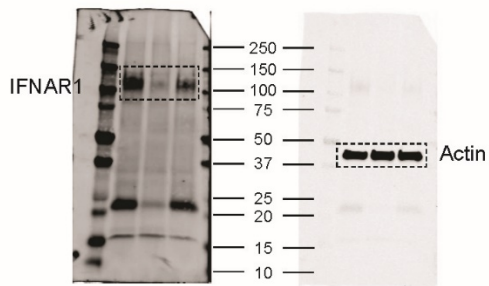
Supplementary Figure 1c



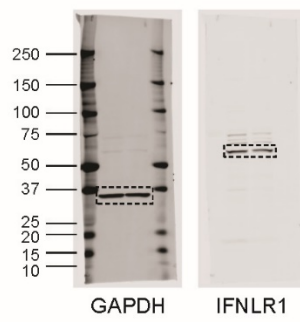
Supplementary Figure 1d



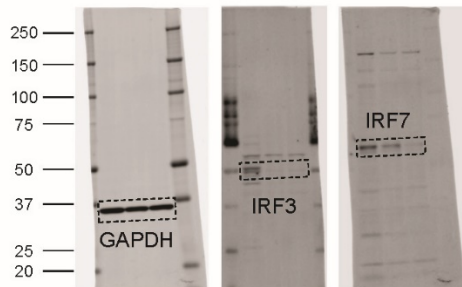
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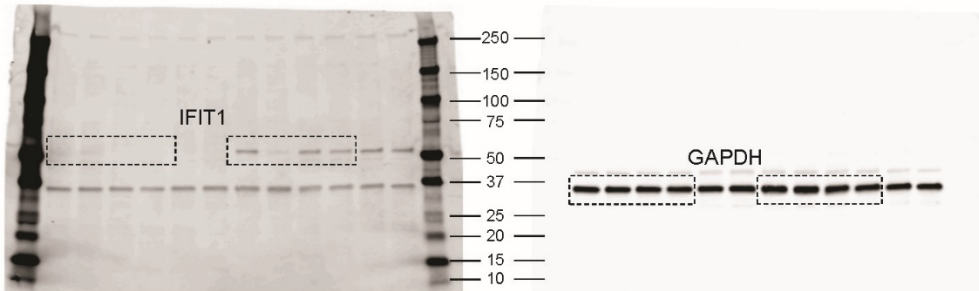
Supplementary Figure 1f



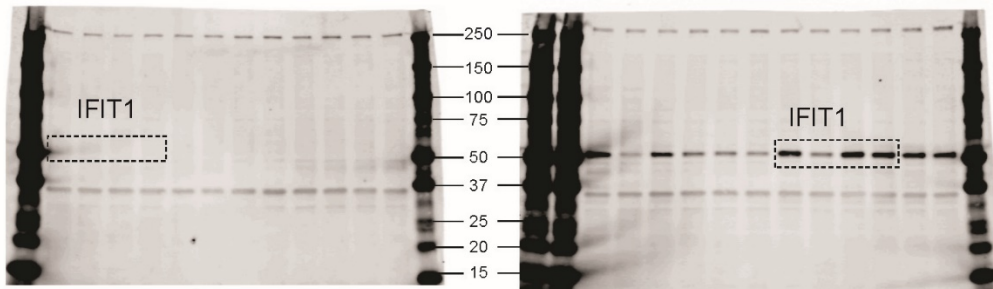
Supplementary Figure 2a



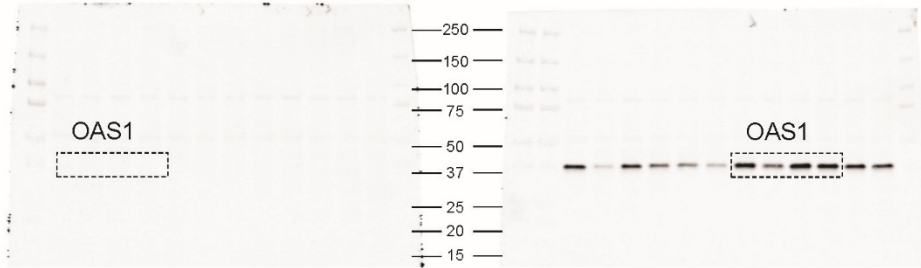
Supplementary Figure 2c



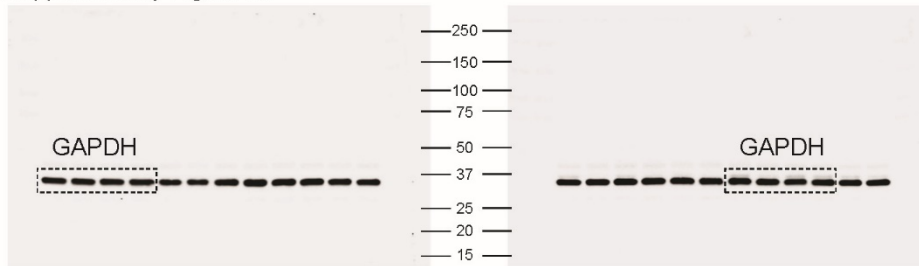
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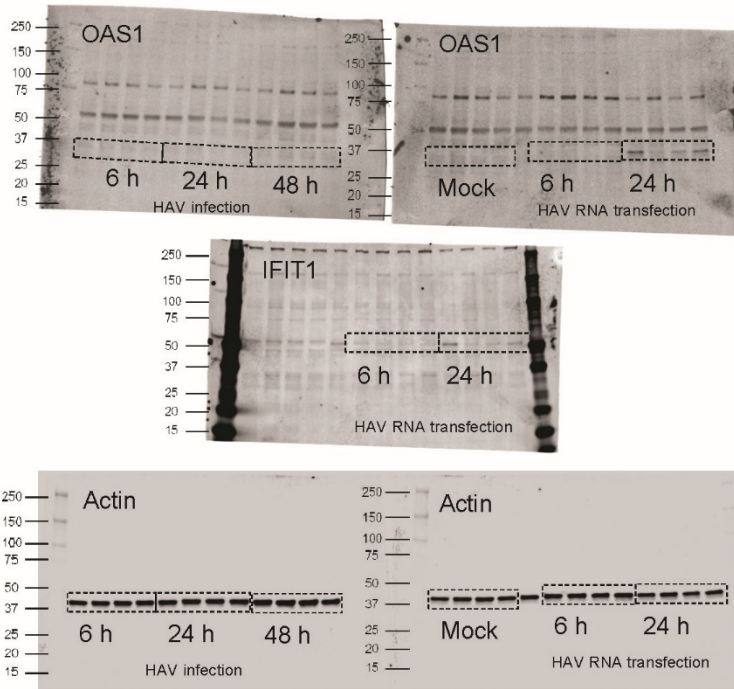
Supplementary Figure 2d



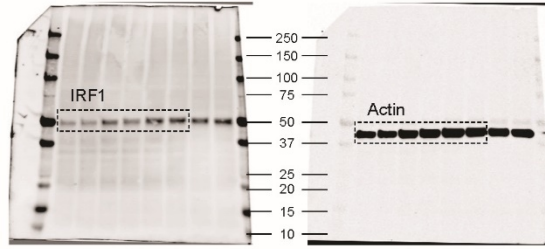
Supplementary Figure 2d



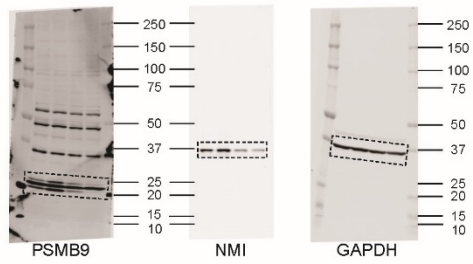
Supplementary Figure 2f



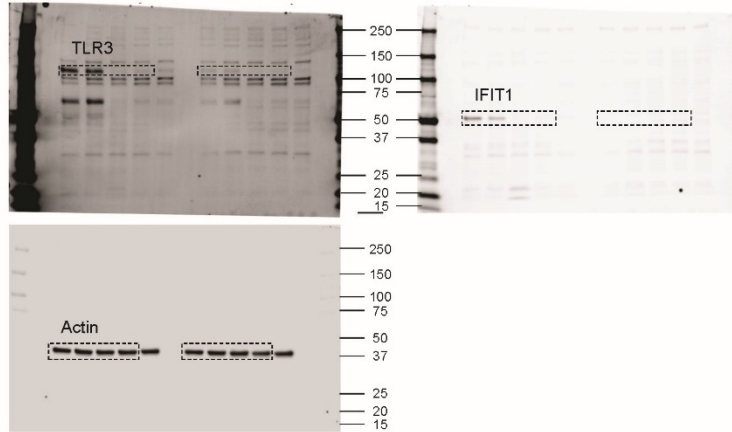
Supplementary Figure 5a



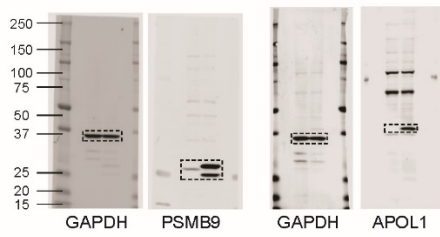
Supplementary Figure 7a



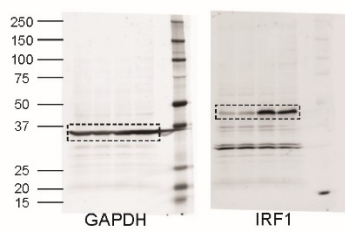
Supplementary Figure 7b



Supplementary Figure 7g



Supplementary Figure 7i



Supplementary Table 1. Short hairpin RNAs used for knockdowns.

Target gene	Target sequence	Sigma catalog# or Clone ID
Non-target control	CAACAAGATGAAGAGCACCAA	SHC002
RIG-I	CCAGAATTATCCCAACCGATA	NM_014314.2-505s1c1
MDA5	CCAACAAGAAGCAGTGTATA	NM_022168.2-1565s1c1
LGP2	GCAAGAAGTGATCCAGAAGTT	NM_024119.1-1483s1c1
MAVS	GCATCTCTTCAATACCCTTCA	NM_020746.1-296s1c1
STING	GCAGAGCTATTTCCCTCCACA	NM_198282.1-1472s1c1
MYD88	GCAGAGCAAGGAATGTGACTT	NM_002468.2-723s1c1
TRIF	CTCCAACCTTTCTGTAGAAGAT	NM_014261.1-588s1c1
IRF3	GCCAACCTGGAAGAGGAATTT	NM_001571.1-265s1c1
IRF7	GCTGGACGTGACCATCATGTA	NM_001572.2-1156s1c1
IRF1	CGTGTGGATCTTGCCACATTT	NM_002198.1-1769s1c1
IFNAR1	GTTGACTCATTACACCATTT	NM_000629.2-496s1c1
IFNLR1	GCCGGAACAAGACCCTATTT	NM_170743.2-512s1c1

Supplementary Table 2. Single guide RNAs used for CRISPR/Cas9 knockouts.

Target gene	Target sequence
Non-target control	CACTCACATCGCTACATGA
IRF1 (#1)	GAAGCATGCTGCCAAGCA
IRF1 (#2)	GAGCCAGATCCCAAGACG
IRF3	AGTATTCTCCAGGGAGG
IFNAR1 (#1)	GCTGCGGACAACACCCA
IFNAR1 (#3)	GTTATGTGGGCTTTGGA
IFNLR1 (#1)	GCAGGAAGGCCATGGCG
IFNLR1 (#2)	GCAGGCCGCTCCAGGTA
MAVS	TATAAGTCCGAGGGCACCTT
STAT1	GCAGCTTGACTCAAAATTCC
RELA (#1)	CAATGATCTCCACATAG
RELA (#3)	CAATGATCTCCACATAG
RARRES3	GGTGATCATCAGTTCTGCGA

Supplementary Table 3. Oligonucleotide primers used for qRT-PCR of IRF1-target host genes.

Gene	Forward	Reverse
RARRES3	GATTTTCCGCCTTGGCTATG	TTGCTCAGGACTGAGAAGAC
PSMB9	GTGGATGCAGCATATAAGCC	AGTGACCAGGTAGATGACAC
APOL6	CTATTGCTCCCAGGCTACGCA	CCCTGCAAGCTCCATTTCGTAGT
GBP3	CGCACAGGAAAATCCTACCT	ACACACCACATCCAGATTCC
ERAP2	GGGCCTCATTACATATAGGGA	ATTCCATTGTGACCAGGTTG
APOL1	ATAATGAGGCCTGGAACGGA	GGTTGTCCAGAGCTTTACGG
SAMD9L	AAGCTCTGAGAGCAGATAGG	TTGAGTTTTGCTGCAGTAGG
UBA7	TGATGCCCTCGATTGTCTTC	ACTTTGAGCAGCTCACAAAC
IFIT3	CTGGCAATTGCGATGTACCA	GTTTCAGGCCCAAGAGAACC
CXCL8	AAGAGCCAGGAAGAAACCAC	CTTGGCAAACTGCACCTTC
NMI	GGAGTTACAAGAGGCTACCA	CGAGCTCACTTCAAACGAAC
TLR3	TAGCAAACACAAGCATTCCGG	AGGAATCGTTACCAACCACA
CFB	TTCCCTGACAGAGACCATAG	CTGTCTGATCCATCTAGCAC
TAP2	CCTCACTATTCTGGTCGTGT	GATCCGCAAGTTGATTTCGAG
IFIT2	GAGAATTGCACTGCAACCATGAG	CGATTCTGAAACTCAGTCCGGTAA
APOL3	ATCCACACAGCTCAGAACAG	CAGCAAATGCCAAGACCAAC
MX1	CAGTTACCAGGACTACGAGA	GGGTGATTAGCTCATGACTG
DDX60	CTTCTATCTGGTTGAACGCT	CAGGGAAGTTGAAATACGCA
ZNF827	AATCGGGCGAGAGAAAACCGAA	GACAGTTGAAAGAGGAGCTCGGAA
CXCL1	ATTCACCCCAAGAACATCCA	CAGGATTGAGGCAAGCTTTC
FYN	CAATGAGTACACAGCAAGAC	AGCTCTGTGAGTAAGATTCC
TENM3	GACAGCTCCAAACAGTTTACCTCA	TGTCTCGCAGGTCATAGCGAA
COL4A1	GCCTGGTGAAGTTTTATTTGAC	ACGCTCTCCTTTCAATCCTAC
COL4A2	GGTTTCTACGGAGTTAAGGG	TTCACCCTTGTACTGATCTG
DPYSL3	GAGCAAACCCGCATGTTGGA	GCAATGGTGTGATGGCACGGAA
ACTB	GACCCAGATCATGTTTGAGACC	GTCACCGGAGTCCATCACGA

Supplementary Table 4. siRNAs used for gene silencing.

Gene Symbol	Gene	Sequence	
RARRES3	NM_004585	GCACUGGGCCUGUAUUA	UAUGGCAAGUCCCGCUGUA
		CAACAGUGCAGAGGUGAAA	CGAAGGAGAUGGUUGGUCA
PSMB9	NM_148954	GCAAAUGUGGUGAGAAUA	GAACCGAGUGUUUGACAAG
		GGCAGCACCUUUUAUCUAUG	ACGUGAAGGAGGUCAGGUA
GBP3	NM_018284	GAGAAGACCCUCACUAGUA	CCACUGAAGUCUAUAUGAA
		GAACAGGCCCGAGUACUAA	CGCAUAAGCUAAAGAUCUA
SAMD9L	NM_152703	GGAAGGGUCUAAACAGUAU	GUAGGAGCAUUACUGUUAA
		GCAACGGGAUGUAGAUUUC	CAGAAAAGGAUUUGCGUAU
IFIT3	NM_001549	GCAAU AUGCUAUGGACUAU	GACUGGCAAUUGCGAUGUA
		GAGACGGAUGUUAUCAGA	UAGAGUGUGUAACCAGAUU
APOL6	NM_030641	GAGAGAAUUUCCAGAUUG	AGAAACACCUUGAAGUAUG
		GAACAACACUGGCGAUGAC	GGGAAGUGGGAGUCGAACA
ERAP2	NM_022350	GAAAGCUGCUGAACUCUUC	GAUCAUCUCUGGCACAACA
		GAGUAGGUCUGAUUCAUGA	GAUCACAUCUGGAUUAUUU
UBA7	NM_003335	GAACAAAGCCCUGGAAGUC	GGGCAGUGCUCACAGUAUUC
		GCACUUCCACCUAUAAA	UGAAGCCUCUGAUUUUGA
APOL1	NM_003661	GUUCCAAGUGGGACAGUA	ACGAUAAAGGCCAGCAGUA
		AGAAUAUAUUGACGGAAGA	AAUGGGAACUGGAGAGUGU
CFB	NM_001710	CGAAGCAGCUCAAUGAAAU	GGAGAUAGAAGUAGUCCUA
		ACACGUACCUGCAGAUUA	ACAGGAAGGGUACCGAUUA
APOL3	NM_145640	GGUCAAGCAGAGAGAACGA	CAACCUUGUAUACGAGUCA
		CAACCAGCAUUGACCGAUU	CCUGUGACCACCUGGCGAA
NMI	NM_004688	CCAAAGAAUCCAGAUUAA	GCUCGAAAGUCCUUAUGA
		CAAGUGAGCUCGAAAGUUC	CGAAAGUCCUUAUGAGAU
MX1	NM_002462	UCACAGAUGUUUCGAUAAA	GAAUGGAAUCAGUCAUGA
		CCACAAAUGGAGUACAUA	CGACAUACCGGAAGACGAA
TLR3	NM_003265	GAAGCUAUGUUUGGAAUUA	GAAGAGGAAUGUUUAAAUC
		GAUCAUCGAUUUAGGAUUG	CAACAUAGCCAACAUAAA
IFIT2	NM_001547	CAAUUGGGUGCUGCUAUA	GGAGAAAGCCCAGGUGUA
		GCAAAAGUCUCCAAGUAA	GAACUAAUAGGACACGCUG
TAP2	NM_018833	GUAACUGGCUUCCUUAUAA	CAUGAAGUCUGUCGCUAUA
		GGAAUUGGAGCAUGGAAUA	GAAACAACGUCUGGCCAUU
DDX60	NM_017631	GAAGGUAAUUGGUCGAGUA	GCACUCACCAUUAUUAUCUA
		GGAGAGAGGUAAUUAUGAUC	AAAUGUCGCUAAUUGCCUA
RPS6KB1	NM_003161	GGACUAUGCAAAGAAUCUA	GGUUUUUCAAGUACGAAAA
IRF7	NM_001572	GUCUAAUGAGAACUCCAGA	GCCUAGAACCCAGUCUAAU
IRF1	NM_002198	UCACAGAUCUGAAGAACAU	CCAAGAACCAGAGAAAAGA
Non-targeting Control	N/A	UAGCGACUAAACACAUCAA	AUGUAUUGGCCUGUAUUAG
		UAAGGCUAUGAAGAGAUAC	AUGAACGUGAAUUGCUCAA

Supplementary Table 5. Differentially expressed genes (> 1.0 log₂) in PH5CH8 cells transduced with 2 independent sgRNAs targeting *IRF1*.

The differential mRNA expression in the sgRNA-expressing cells grown in triplicate compared to control was determined using DESeq2. The p-values were determined using the negative binomial Wald test. The p-values were adjusted using false discovery rate (FDR) correction.

a. Differentially expressed genes (> 1.0 log₂) in PH5CH8 cells transduced with *IRF1* #1 sgRNA.

Down-regulated genes				Up-regulated genes			
Rank	Gene	Log2 Foldchange	padj	Rank	Gene	Log2 Foldchange	padj
1	RARRES3	-4.30605607	0	51	BIRC3	-1.173786664	2.40E-28
2	PSMB9	-3.070227661	4.01E-141	52	ATP10D	-1.171899468	3.06E-22
3	APOL6	-2.618325001	3.61E-173	53	IFIH1	-1.171377019	7.87E-18
4	GBP3	-2.564265161	2.41E-85	54	SOD2	-1.168138821	9.89E-75
5	ERAP2	-2.545561012	7.42E-212	55	HPGD	-1.141701789	6.97E-38
6	APOL1	-2.518894585	0	56	IL15	-1.124268707	3.62E-17
7	SAMD9L	-2.509506919	2.56E-81	57	OAS1	-1.121088971	1.04E-20
8	UBA7	-2.449501879	6.30E-135	58	FOSL1	-1.106411339	8.16E-48
9	IFIT3	-2.339444768	6.62E-103	59	OAS3	-1.105874085	1.41E-66
10	CXCL8	-2.238182461	1.24E-117	60	TNFAIP3	-1.099669587	1.88E-28
11	NMI	-2.150694321	1.51E-78	61	CXCL2	-1.094667802	1.36E-15
12	TLR3	-2.085901887	2.44E-54	62	TNFRSF14	-1.070706215	1.03E-15
13	CFB	-1.949049961	1.39E-78	63	NFIX	-1.052325125	5.38E-15
14	C3	-1.917893461	6.57E-118	64	TRABD2A	-1.029835611	3.43E-13
15	MEG3	-1.893786333	1.29E-44	65	TRANK1	-1.024365993	2.22E-26
16	PSMB8	-1.885590966	1.53E-135	66	TM4SF18	-1.023442793	2.86E-16
17	TAP2	-1.876453474	3.35E-160	67	GLUL	-1.02290644	1.20E-36
18	FGB	-1.870468009	5.95E-92	68	ACTA2	-1.019950576	7.18E-13
19	IFIT2	-1.793546489	1.29E-52	69	STARD4	-1.011659171	1.78E-14
20	APOL3	-1.754325695	3.44E-38	70	OSBPL6	-1.011470949	1.11E-14
21	DDX60	-1.750967907	1.70E-44	71	DTNA	-1.008331529	1.53E-12
22	MX1	-1.748456819	7.04E-56				
23	PARP10	-1.706256534	6.50E-75				
24	ZNF827	-1.657126982	1.64E-34				
25	CXCL1	-1.654437285	1.46E-49				
26	IRF1	-1.620030816	4.90E-125				
27	FYN	-1.584149049	3.32E-38				
28	BTN3A3	-1.561734794	1.23E-66				
29	UBE2L6	-1.555460225	7.92E-70				
30	AASS	-1.555233906	8.60E-30				
31	PARP14	-1.525757089	5.70E-120				
32	HLA-B	-1.499518883	5.89E-83				
33	UBD	-1.489687126	6.91E-28				
34	VCAM1	-1.486441985	4.53E-119				
35	PARP12	-1.46314127	5.34E-66				
36	PSMB10	-1.433041032	5.56E-45				
37	ERAP1	-1.410032105	1.80E-63				
38	PSMB8-AS1	-1.386597048	1.39E-23				
39	TNFAIP2	-1.337873899	8.94E-171				
40	TRIM22	-1.328653068	7.17E-22				
41	FGG	-1.287772344	2.18E-20				
42	ACSL5	-1.284806127	2.98E-24				
43	LGALS9	-1.266127198	7.66E-20				
44	CCL2	-1.263565625	8.71E-65				
45	CTSS	-1.253522216	3.32E-21				
46	DDX60L	-1.238249346	1.04E-20				
47	MUC5AC	-1.197902994	2.50E-18				
48	DTX3L	-1.195713255	3.57E-64				
49	NT5E	-1.190971531	5.81E-26				
50	TAP1	-1.183769535	4.20E-72				

b. Differentially expressed genes (> 1.0 log₂) in PH5CH8 cells transduced with *IRF1* #2 sgRNA.

Down-regulated genes				Up-regulated genes			
Rank	Gene	Log2 Foldchange	padj	Rank	Gene	Log2 Foldchange	padj
1	RARRES3	-3.9797151	0	51	PARP14	-1.31951145	2.52E-91
2	PSMB9	-3.04157472	8.92E-125	52	LRP3	-1.3062438	4.12E-20
3	FYN	-2.71569318	2.62E-81	53	BMP5	-1.28266879	1.52E-67
4	GBP3	-2.62753909	3.15E-74	54	DPYD	-1.27776913	2.74E-25
5	SAMD9L	-2.55223866	2.28E-69	55	NFIX	-1.27482521	6.81E-18
6	EPHA3	-2.38994137	4.93E-171	56	FBN1	-1.26243065	2.79E-40
7	CXCL8	-2.38385062	1.04E-123	57	OSBPL6	-1.24682701	8.68E-16
8	IFIT3	-2.32135177	1.57E-91	58	PSMB8	-1.23399641	2.20E-65
9	CFB	-2.16384796	5.17E-88	59	FGG	-1.20962596	2.21E-14
10	APOL3	-2.16271531	3.06E-43	60	CXCL2	-1.20073982	2.52E-15
11	MX1	-2.13538021	1.05E-71	61	DMKN	-1.19809836	5.65E-51
12	UBA7	-2.08939534	3.48E-99	62	ELOVL7	-1.19603982	2.35E-14
13	ERAP2	-2.04585084	1.11E-149	63	BCAT1	-1.19072612	5.68E-15
14	BCHE	-2.01280126	4.23E-122	64	DDX26B	-1.18319328	2.66E-13
15	APOL6	-1.97748878	6.57E-117	65	TRANK1	-1.17545729	2.57E-30
16	APOL1	-1.91956954	1.93E-270	66	ACSL5	-1.16641946	1.41E-17
17	CDH6	-1.85291099	1.93E-53	67	SLC16A7	-1.16012119	1.54E-16
18	CXCL1	-1.8376753	1.49E-55	68	PCDH18	-1.14546803	7.43E-13
19	MEG3	-1.83584728	4.08E-34	69	MARCKS	-1.14163347	1.72E-30
20	ZNF827	-1.7999967	1.20E-32	70	BCO1	-1.10058789	2.39E-11
21	TLR3	-1.77443867	3.89E-33	71	RNF217	-1.09514509	2.48E-11
22	AMPH	-1.77178777	3.33E-45	72	PCDH10	-1.07378563	1.18E-12
23	NMI	-1.74529971	1.91E-56	73	DDX60L	-1.07228272	2.53E-12
24	PSMB10	-1.743854	2.90E-58	74	TRABD2A	-1.0700364	1.80E-11
25	TMPRSS15	-1.72236919	1.43E-131	75	GREM1	-1.05714764	6.94E-60
26	UBE2L6	-1.71979678	2.39E-79	76	HMCN1	-1.05126845	2.89E-83
27	DDX60	-1.69922312	5.41E-37	77	IL15RA	-1.04574927	5.04E-12
28	PVRL3	-1.68958306	2.62E-33	78	IFIH1	-1.04323298	3.07E-10
29	IFIT2	-1.67977636	1.40E-41	79	SLITRK3	-1.03910218	1.11E-10
30	UBD	-1.6555172	2.47E-25	80	CD74	-1.03828198	3.28E-10
31	FGB	-1.61005657	2.42E-65	81	ATP10D	-1.02983714	8.96E-16
32	TAP2	-1.57984539	2.36E-136	82	HIST1H1C	-1.02772643	4.08E-34
33	LGALS9	-1.56133472	2.05E-23	83	PGM5	-1.02542065	3.93E-10
34	PCDH7	-1.53276464	5.30E-23	84	PTX3	-1.02480435	1.43E-10
35	BTN3A3	-1.50838594	1.84E-58	85	ST3GAL1	-1.0215178	1.91E-17
36	VANGL2	-1.50397963	7.12E-23	86	MX2	-1.01047767	1.19E-09
37	C3	-1.48301596	6.14E-72	87	HLA-B	-1.00132638	1.25E-40
38	IL15	-1.46681703	5.72E-21	88	DTNA	-1.00092823	1.55E-09
39	CTSS	-1.45305055	9.51E-23	89	KCTD12	-1.00005731	1.88E-09
40	KIAA1211	-1.43382356	7.58E-20				
41	PSMB8-AS1	-1.42295053	2.25E-19				
42	TRIM22	-1.4155635	9.97E-19				
43	TNFAIP2	-1.39922336	8.11E-194				
44	PCOLCE2	-1.39911257	1.92E-18				
45	PTN	-1.34105797	2.24E-41				
46	VCAM1	-1.33887411	1.01E-102				
47	CBLN2	-1.33755103	4.65E-35				
48	PIK3AP1	-1.32320088	2.73E-19				
49	CCL2	-1.31961393	5.60E-67				
50	PARP10	-1.31952853	5.93E-46				
1	TENM3	2.59907996	8.19E-171				
2	DPYSL3	2.3470478	8.35E-240				
3	COL4A2	1.98925264	1.00E-278				
4	CPS1	1.87126782	3.85E-38				
5	ADAP2	1.68675434	1.63E-29				
6	ST6GAL2	1.65957594	1.54E-28				
7	COL4A1	1.63883655	4.11E-171				
8	TRPM2	1.62428886	7.93E-25				
9	APBB1IP	1.58385023	2.14E-23				
10	PLAC8	1.50945035	5.01E-36				
11	CDA	1.49642137	1.08E-34				
12	L1CAM	1.46939018	8.21E-198				
13	MYO7A	1.41126263	8.11E-29				
14	TIMP3	1.40930019	4.88E-53				
15	MALRD1	1.38551206	9.89E-40				
16	GADL1	1.38265219	3.32E-20				
17	FMOD	1.34811809	3.36E-22				
18	F10	1.34602364	2.66E-17				
19	SPOCK1	1.34139016	3.17E-99				
20	NOTUM	1.32299038	6.06E-20				
21	ITGA11	1.3187266	3.42E-16				
22	HOXC12	1.28245386	1.75E-15				
23	FAM49A	1.26821737	3.86E-15				
24	TNC	1.26275069	2.39E-106				
25	PTGS1	1.2390419	1.37E-21				
26	ADM2	1.23305933	9.56E-15				
27	TCF21	1.23102459	2.40E-14				
28	APCDD1L-AS1	1.22639092	4.29E-65				
29	NDRG1	1.20209538	5.54E-62				
30	B3GALT5	1.18919321	6.85E-16				
31	ARFGEF3	1.18884895	1.24E-13				
32	APCDD1L	1.1668644	1.84E-58				
33	PCDHGA4	1.13357058	2.43E-12				
34	CPM	1.12043845	3.43E-13				
35	ENG	1.11392435	1.46E-45				
36	IL20RA	1.11267656	6.06E-12				
37	FBLN2	1.1108584	1.49E-41				
38	PALMD	1.0906187	5.06E-12				
39	PDE1C	1.07482238	1.09E-110				
40	B4GALNT2	1.07429855	7.28E-14				
41	ACSS1	1.06358194	4.66E-20				
42	MFGE8	1.05614296	2.38E-90				
43	TNS4	1.0509688	5.34E-16				
44	TLN2	1.04209086	3.45E-45				
45	CTSH	1.03611327	1.45E-41				
46	ALPK2	1.03509411	2.10E-10				
47	SARDH	1.02997474	4.28E-12				
48	ALPPL2	1.02084613	4.38E-29				

Supplementary Table 6. Gene Ontology (GO) analysis and functional annotation of IRF1-regulated genes.

Gene ontology enrichment analysis was performed using DAVID 6.8. The threshold of EASE Score, a modified Fisher Exact P-Value, was used for gene-enrichment analysis.

Term	%	p-value	Genes
inflammatory response	18.52	1.53E-06	CXCL1, APOL3, NMI, CCL2, C3, CXCL2, CXCL8, TLR3, IL15, LGALS9
defense response to virus	12.96	9.13E-06	IFIT3, IFIT2, DDX60, TLR3, MX1, TRIM22, GBP3
response to virus	11.11	1.84E-05	IFIT3, IFIT2, IFIH1, DDX60, MX1, TRIM22
immune response	16.67	3.12E-05	CXCL1, CCL2, C3, CXCL2, CXCL8, IL15, HLA-B, CTSS, TRIM22
type I interferon signaling pathway	9.26	3.87E-05	IFIT3, IFIT2, HLA-B, MX1, PSMB8
innate immune response	14.81	2.65E-04	IFIH1, APOL1, FYN, FGB, DDX60, TLR3,
proteolysis involved in cellular protein catabolic process	7.41	3.91E-04	PSMB10, CTSS, PSMB8, PSMB9
chemotaxis	9.26	4.72E-04	CXCL1, CCL2, CXCL2, CXCL8, LGALS9
signal transduction	22.22	5.03E-04	CXCL1, APOL3, FGG, CCL2, FGB, C3, TENM3, CXCL8, TLR3, IL15, MX1, DTNA
antigen processing and presentation of exogenous peptide antigen via MHC class I, TAP-dependent	7.41	8.70E-04	PSMB10, HLA-B, PSMB8, PSMB9
cell chemotaxis	7.41	9.53E-04	CXCL1, VCAM1, CCL2, CXCL2
adaptive immune response	9.26	9.74E-04	FYN, FGB, TAP2, ERAP2, CTSS
chemokine-mediated signaling pathway	7.41	0.001231285	CXCL1, CCL2, CXCL2, CXCL8
interferon-gamma-mediated signaling pathway	7.41	0.001231285	VCAM1, NMI, HLA-B, TRIM22
positive regulation of I-kappaB kinase/NF-kappaB signaling	9.26	0.001330272	APOL3, FYN, UBD, TRIM22, LGALS9
lipid transport	7.41	0.001498741	APOL3, APOL1, OSBPL6, APOL6
viral process	11.11	0.001904387	PSMB10, VCAM1, FYN, HLA-B, PSMB8,
positive regulation of neutrophil chemotaxis	5.56	0.001932233	CXCL1, CXCL2, CXCL8
negative regulation of type I interferon production	5.56	0.003583763	IFIH1, UBA7, UBE2L6
antigen processing and presentation of peptide antigen via MHC class I	5.56	0.003583763	TAP2, ERAP2, HLA-B
stimulatory C-type lectin receptor signaling pathway	7.41	0.003762113	PSMB10, FYN, PSMB8, PSMB9
lipoprotein metabolic process	5.56	0.005704509	APOL3, APOL1, APOL6
MAPK cascade	9.26	0.007600966	PSMB10, CCL2, FYN, PSMB8, PSMB9
T cell receptor signaling pathway	7.41	0.009716944	PSMB10, FYN, PSMB8, PSMB9
regulation of cellular amino acid metabolic process	5.56	0.010094659	PSMB10, PSMB8, PSMB9
antigen processing and presentation	5.56	0.01166882	HLA-B, CTSS, PSMB8
blood coagulation, fibrin clot formation	3.70	0.011858397	FGG, FGB
cellular response to interferon-gamma	5.56	0.012493782	CCL2, TLR3, LGALS9
response to lipopolysaccharide	7.41	0.012816289	CXCL1, VCAM1, CXCL2, LGALS9
negative regulation of angiogenesis	5.56	0.014664146	COL4A2, CCL2, MEG3
modification-dependent protein catabolic process	3.70	0.014801397	UBA7, UBE2L6
detection of virus	3.70	0.014801397	IFIH1, TLR3
positive regulation of ERK1 and ERK2 cascade	7.41	0.015239694	FGG, CCL2, FGB, LGALS9
proteolysis	11.11	0.016165826	C3, CFB, TRABD2A, UBD, ERAP2, CTSS
NIK/NF-kappaB signaling	5.56	0.016508931	PSMB10, PSMB8, PSMB9
ISG15-protein conjugation	3.70	0.017735806	UBA7, UBE2L6
negative regulation of ubiquitin-protein ligase activity involved in mitotic cell cycle	5.56	0.018946536	PSMB10, PSMB8, PSMB9
cellular response to interleukin-1	5.56	0.018946536	CCL2, FGB, CXCL8
positive regulation of inflammatory response	5.56	0.019961569	CCL2, TLR3, IL15
extracellular matrix organization	7.41	0.020540948	VCAM1, COL4A2, FGG, FGB
antigen processing and presentation of endogenous peptide antigen via MHC class I	3.70	0.020661649	TAP2, ERAP2
positive regulation of apoptotic cell clearance	3.70	0.020661649	CCL2, C3
positive regulation of ubiquitin-protein ligase activity involved in regulation of mitotic cell cycle transition	5.56	0.021526047	PSMB10, PSMB8, PSMB9
anaphase-promoting complex-dependent catabolic process	5.56	0.023139967	PSMB10, PSMB8, PSMB9

Supplementary Table 6. (continued)

positive regulation of peptide hormone secretion	3.70	0.023578952	FGG, FGB
plasminogen activation	3.70	0.026487737	FGG, FGB
response to molecule of bacterial origin	3.70	0.026487737	CXCL2, CXCL8
cellular response to interferon-alpha	3.70	0.026487737	IFIT3, IFIT2
angiogenesis	7.41	0.028671722	COL4A2, CCL2, CXCL8, TNFAIP2
positive regulation of neuron projection development	5.56	0.028864466	FYN, TENM3, DPYSL3
cell-matrix adhesion	5.56	0.029465192	VCAM1, FGG, FGB
negative regulation of cell proliferation	9.26	0.029944147	CXCL1, IFIT3, RARRES3, MEG3, CXCL8
Wnt signaling pathway, planar cell polarity pathway	5.56	0.030681622	PSMB10, PSMB8, PSMB9
positive regulation of heterotypic cell-cell adhesion	3.70	0.032279854	FGG, FGB
PERK-mediated unfolded protein response	3.70	0.035163235	CCL2, CXCL8
regulation of mRNA stability	5.56	0.037717825	PSMB10, PSMB8, PSMB9
protein polymerization	3.70	0.038038195	FGG, FGB
complement activation, alternative pathway	3.70	0.038038195	C3, CFB
response to ethanol	5.56	0.039057882	VCAM1, CCL2, FYN
cellular response to tumor necrosis factor	5.56	0.042486433	VCAM1, CCL2, CXCL8
platelet activation	5.56	0.04602387	FGG, FYN, FGB
tumor necrosis factor-mediated signaling pathway	5.56	0.048197	PSMB10, PSMB8, PSMB9
positive regulation of canonical Wnt signaling pathway	5.56	0.049666362	PSMB10, PSMB8, PSMB9
cellular protein complex assembly	3.70	0.05228754	FGG, FGB
cellular response to platelet-derived growth factor stimulus	3.70	0.05228754	CCL2, FYN
positive regulation of NF-kappaB transcription factor activity	5.56	0.059601848	TLR3, TRIM22, LGALS9
fibrinolysis	3.70	0.06073764	FGG, FGB
positive regulation of exocytosis	3.70	0.06073764	FGG, FGB
positive regulation of NF-kappaB import into nucleus	3.70	0.06073764	TLR3, LGALS9
negative regulation of gene expression	5.56	0.062786869	FYN, PARP10, LGALS9
maternal process involved in female pregnancy	3.70	0.071889672	CCL2, LGALS9
toll-like receptor signaling pathway	3.70	0.077416922	TLR3, CTSS
positive regulation of interferon-beta production	3.70	0.077416922	IFIH1, TLR3
negative regulation of endothelial cell apoptotic process	3.70	0.080168437	FGG, FGB
negative regulation of canonical Wnt signaling pathway	5.56	0.084804646	PSMB10, PSMB8, PSMB9
regulation of complement activation	3.70	0.085647363	C3, CFB
cellular response to fibroblast growth factor stimulus	3.70	0.085647363	CCL2, CXCL8
aging	5.56	0.086585008	VCAM1, CCL2, IL15
positive regulation of substrate adhesion-dependent cell spreading	3.70	0.091094304	FGG, FGB
positive regulation of vasoconstriction	3.70	0.091094304	FGG, FGB
JAK-STAT cascade	3.70	0.091094304	NMI, CCL2
protein ubiquitination	7.41	0.091143526	UBA7, UBD, UBE2L6, TRIM22
negative regulation of extrinsic apoptotic signaling pathway via death domain receptors	3.70	0.093805836	FGG, FGB
regulation of immune response	5.56	0.098426464	VCAM1, C3, HLA-B
Fc-epsilon receptor signaling pathway	5.56	0.098426464	PSMB10, PSMB8, PSMB9

Supplementary Table 7. Differentially expressed genes (> 0.9 log2) in PH5CH8 cells transduced with *IRF3* sgRNA.

The differential mRNA expression in the sgRNA-expressing cells grown in triplicate compared to control was determined using DESeq2. The p-values were determined using the negative binomial Wald test. The p-values were adjusted using FDR correction.

Down-regulated genes				Up-regulated genes			
Rank	Gene	Log2 Foldchange	padj	Rank	Gene	Log2 Foldchange	padj
1	FGB	-2.43110474	5.88E-180	1	COL11A1	1.451866601	1.55E-108
2	FBN1	-1.89904401	3.17E-115	2	COL4A2	1.040039013	3.33E-100
3	FYN	-1.30487143	1.28E-42	3	PLAC8	0.927984568	7.00E-22
4	MEG3	-1.22357953	5.77E-37	4	PIEZO2	0.921067089	1.01E-20
5	PTN	-1.18972062	1.47E-49				
6	DSE	-1.06998253	7.70E-42				
7	HPGD	-1.01419017	3.89E-38				
8	ZNF827	-0.98038598	3.29E-23				
9	FGG	-0.97147061	7.62E-25				
10	C3	-0.95927482	1.92E-43				
11	ADAMTS1	-0.9025002	4.15E-25				

Supplementary Table 8. IRF1-binding sites identified within the transcription regulatory region of IRF1 effector genes.

IRF1-consensus sites aligning with the sequence Logo of the JASPAR IRF1 matrix (Matrix ID: MA0050.2)¹ are shown in **bold**. IRF1-ChIP sequence results were obtained from the UCSC Genome Browser².

Gene	IRF1-ChIP sequence	position
RARRES3	CCCTTCGACTCTGGCTGCTCCCAAGGTGGCTTTAAAGCACCAATGAGTCCATGGCTTGTGTAAGAAATGATTAGTC CTTCCATCTAGAGAAATAGCTCCTTTTTAAACAGTTGTCTCTTTTAAACAGTGTTTAGTATTAAAGTGAGGTTGAAACA GTGTCAAAAG GAAAGTGAAAGTGA AATTCTCTCCTCAGCATAAAAGCTGATCCACAAACAAGAGGAGCACCAGA CCTCCTTTGGCTTCGAGATGGCTTCGGTAAGTTTCCAGGGCTTTGCATTACTGACTCTACAGCAGTTGGGCAGC TCCCCCTAGGAAAGGCCTCAGTCCAGGCTCCTGGCTTGGGCACACAGCT	chr11:63304093- 63304448
PSMB9	GCCCCGGTGGGGCCTGAAGTCCGGGTACCGCCGAGTCTCCCTACTGGCGGCTGGGGGAGGGAACGAGGG CGGGGCTCTCGAAAGTCCAGGAACAGGCTGATCTGCGCTGGCGAGAAGCTCAGCCATTTAGGG GAAAGCG AAATCGAAAGC GGCCGCCTGCTCACTAGATAACGCCTACTTCCAAAAGTGGCCTGCCAGACTATTTTGGTAGCAA GCGTGAATCAGATCTGAGAATCTCGGGAGCAGCCCTGGTGCCCAATTTTCTCCATCACGCACACCCTTCTCGC CTCTCCTGCCTCTGCCTTTCCACTTGCACAGTTTTCCACCCAGCCTCAGGGCGGGGCTGCCTCGTCACTT GTCTCGGGCAGATCTGCCCTACACACGTTAGCGCCGCGCAAGCAGCCCCGACGCCAGCCAGCGCCTCCT GGCGGCCCGGAAGGGGGGGGCTGTGGCTGCGCTTGTGCGCTGTCCAGTTGGAACCAAGTCCCA GGCGCGAGGAGAGCGGTGCCTTGCAGGATGCTGCGGGCGGAGCACCAACCGGGACTTACCCCGGGCGG GAGAAGTCCACA	chr6:32821462- 32822061
GBP3	GTTGTTTCTGCTCACTTCTTTTTCTTCGCTGGATCGCTGGACTTTTATTTACCCCTTCAGTGTGTGAGCTTTCT GGATTTTCTCAGTGATCAAATAATTAGAAGTTAAGCAACCTTTGTAATGGCTTTCAGAGCCTAAT GAAACTGAAAGT ACTTCTTCAAGGAAGTACTCAGTAACCATAAATGCAATTTCTGGATTCTGCTAGTAGGAGGTTTAAAGTCAAGTT TCAAAGTTTTTTTGTGGAAGAGATCTTAGAGACCATTATTGTTTTAAAACATGTCCATTAGGTATTGAAAAAA	chr1:89488395- 89488704
SAMD9L	CTCTCAGGGACAAGCCACCCCATCTTTGAGAGACCCTCAGCAACACCCTGATATCCATGCCCTAGGGAGGTGT TCTGCTCTGCAGGATTCTTAGAACTGATGTAGGGGAAACACACTTCAGAATCTGGCTGTAGCCAGGAGAGCTACC CACACCCTCCTGCATAGTCTGGCAGACAGAAGCCACACAAGCAAG TAGTTTCGTTTTTC CTGAAGAACACTTTGC ATTTTTTTCTTAGTTTTCAACCAGATTGCTGGATAAGATGTATGGAATGAAATACTTTAATAGAATAATATTAGCCTC TGCAGAGTATTAACCTTGATAAAATGTAAGTTTTAATAACATCTTACGTTATGAAGACAGAATTT	chr7:92776771- 92777145
IFIT3	CTCTCAGGGACAAGCCACCCCATCTTTGAGAGACCCTCAGCAACACCCTGATATCCATGCCCTAGGGAGGTGT TCTGCTCTGCAGGATTCTTAGAACTGATGTAGGGGAAACACACTTCAGAATCTGGCTGTAGCCAGGAGAGCTACC CACACCCTCCTGCATAGTCTGGCAGACAGAAGCCACACAAGCAAG TAGTTTCGTTTTTC CTGAAGAACACTTTGC ATTTT TTTTCTTAGTTTTCAACCAGATTGCTGGATAAGATGTATGGAATGAAATACTTTAATAGAATAATATTAGCCTC TGCAGAGTATTAACCTTGATAAAATGTAAGTTTTAATAACATCTTACGTTATGAAGACAGAATTT	chr7:92776771- 92777145
APOL6	CTCTCAGGGACAAGCCACCCCATCTTTGAGAGACCCTCAGCAACACCCTGATATCCATGCCCTAGGGAGGTGT TCTGCTCTGCAGGATTCTTAGAACTGATGTAGGGGAAACACACTTCAGAATCTGGCTGTAGCCAGGAGAGCTACC CACACCCTCCTGCATAGTCTGGCAGACAGAAGCCACACAAGCAAG TAGTTTCGTTTTTC CTGAAGAACACTTTGC ATTTTTTTCTTAGTTTTCAACCAGATTGCTGGATAAGATGTATGGAATGAAATACTTTAATAGAATAATATTAGCCTC TGCAGAGTATTAACCTTGATAAAATGTAAGTTTTAATAACATCTTACGTTATGAAGACAGAATTT	chr7:92776771- 92777145
ERAP2	CATACCCCATATAGTCCATCCTATAACACAGCCAGGACAGAGACGAGAGACTCAGGCCTCCTGACTTGGATTCTG CTCTTTCACCTCCTTGTTCATCCAATTAGAGAACTGGCAAAAAG GAAACTGAAAGT GACAGCTGGAGCCCATGAT TTCCTGGAAGAGCCCTAGAGCTTTGCTTTTTCTCTCCTGCAGCACTTAACCGAAACCAGTTTTGCAATCAATCCTG TTCAAAGGCCACCCTACTCTCCTATCGTCTTCTCCAGCCAGACACTCACAGCCCTGCCAGACCAGGGGA CCTCGG	chr22:36044284- 36044593
UBA7	GAACAGTAGGCTGCAGCGCTCAGAGATAGGGTCTTTGTAGGTGGCGGTGACAGTAGGGGCCAGTCCCTGCT GTAGCCAGTGCAAACAGGAACCAAGGCCAAGCAATAAGGGACGCTGCTGGTCAACAGCTCTCTTCTGGAGAAA AGAAAAGTGA AAGTTAAACTATGCTCTGAGCTGGCTCCTGATCCTGCCTCCAGACGCCAGCCCCAGACAGGCCAT TCAGGGTCTAAAACCTGGGATGAGTTCAGGACTCTCAAGAGGTGATCAGTCTCTGAGTGCAGACCTGAGGGTG GGAGGCATGGGGCAGCCACATTCACACATGTTCTATTTTCTTTTAGACTTTTATTT	chr3:49851237- 49851592

APOL1	ACCCCCAGCCCTGAGGATGCGAGGCAGGTGGGTTGGATGAGAGGGATCTGGATGTCTGGTCTCAGGCTGCTCCT CTAAGGGCAGCAGCAAGGAGGGTGGGGCTGGACTGAAGGTGGAGGGGAGCGTGTTCCTGTGCTTGGTTCATGA GCTGCTGGGAAGTTGTG <u>ACTTTCACCTTC</u> CCTTTTCGAATTCCTCGGTATATCTTGGGACTGGAGGACCTGTCTGG TTATTATACAGACGCATAACTGGAGGTGGGATCCACACAGCTCAGAACAGCTGGATCTTGCTCAGTCTCTGCCAGG GGAAGATTCT	chr2:36648954- 36649263
CFB	TTCCCCCCGCACCAACTCACCAGCCGCGGGGGAGACCCGAGCTCCGGGACTTCTGCTTCAGCGTGAGG TCCGCTCCGTCTCTCCAACCTCGCTACCGGCTCTGGTCCGCCAGCTACGCTCGGCCAGGGCGGGCCTCAGGG CTCGGGCAGCTTTCG <u>CTTTCGCTTC</u> CCCAGCCAAGGCCCTTATTCTGGGCTGGGCCCGGGAGGGGGCGCGC GAGACCCGACAGCGGAAGTGGAGCCGAACTCTGGTTCGCACTGTACAGGCTGCAATGAGTCTCACTCGC CTTTAGTGGCGTTACTCTGGGATATAAACTGCAAAAATGTTTCTTTATCATTAAAGTAAATACAGT	chr6:32806409- 32806769
APOL3	GAACAGTAGGCTGCAGCGCTCAGAGATAGGGTCTTTGTGTAGGTGGCGGTGACAGTAGGGCCAGTCCCTGCT GTAGCCAGTGCAAACAGGAACCAAGGCCAAGCGAATAAGGGACGCTGCTGGTCCAGCTCTCTTCTGGAGAAA AG <u>AAAAGTGAAG</u> TTAAACTATGCTCTGAGCTGGCTCCTGATCCTGCCTCCAGACGCCAGCCCCAGACAGGCCAT TCAGGGTCTAAACCTGGGATGAGTTCAGGACTCTCAAGAGGTGATCAGTCTCTGAGTGTACAGCTGAGGGTG GGAGGCATGGGCAGCCACATTCACACATGTTCTATTTCCTTTTAGACTTTTATT	chr3:49851237- 49851592
NMI	TTATGTTAGTTTATATTGCAAAGGAGAATTAAGGCTGCAGATTGAATTAAGGTTGCTAATCAGCTTGTCTTTAAATATG GAGAGCATCTGGATTATCTGTGGGAGCCAGTGAATCATGAGGCTACTT <u>AAAAGTGAAG</u> CGGAAGACAGAAG AAGAGTCAAGAGTGAATGTGACCCCGAAGAACTTTCAGAGGCGCAATGTTGCTGGCCCTGAAGATGAGGAA GGGCTGCTGAGCCAAATAAGGTAGGTGGCCTCCGGAAGATGAAAAGAGGATCACCCCAAGACTTCCAGAAA GAAGCAA	chr2:152144687- 152144996
MX1	GAACAGTAGGCTGCAGCGCTCAGAGATAGGGTCTTTGTGTAGGTGGCGGTGACAGTAGGGCCAGTCCCTGCT GTAGCCAGTGCAAACAGGAACCAAGGCCAAGCGAATAAGGGACGCTGCTGGTCCAGCTCTCTTCTGGAGAAA AG <u>AAAAGTGAAG</u> TTAAACTATGCTCTGAGCTGGCTCCTGATCCTGCCTCCAGACGCCAGCCCCAGACAGGCCAT TCAGGGTCTAAACCTGGGATGAGTTCAGGACTCTCAAGAGGTGATCAGTCTCTGAGTGTACAGCTGAGGGTG GGAGGCATGGGCAGCCACATTCACACATGTTCTATTTCCTTTTAGACTTTTATT	chr3:49851237- 49851592
TLR3	GTGAGGTCCCACTTTCAACTTTAGCTGTTGCTAAATCTGTGACCCCTTCAATGAAATCCAAGGATCTCAGCTAAA AAAAGTTAAATAAAATAAAACTAGGTGTTTTTCAGAGCGGTTTGAACGCCTCTCTGAGTTGTCAGAGATTGT TTTTGTTTTCTCCCTTTGCCCTTCTTGAATGCACCAAATAAAAGCATTTTTTTTCAAGCTTTA <u>CTTTCACCTTC</u> G GAGTGCCGTCTATTTGCCACACACTTCCCTGATGAAATGTCTGGATTTGGACTAAAGAAAAAGGAAAGGCTAGCA GTCATCCAAGTAAGTGAAGGTGTTCACTTTACAGTCTTACTGGGCAGGGTCTCTCTTGTGAGTAGATTTG	chr4:186990085- 186990465
IFIT2	CCCCAGACCCATCTTAAAGTGAAGCACCAGGCCGATGAAACATCCCTCTCTGCTGCCTTCTTCTCTGATCACAAC TCAGCTCCGGAGGAAAAAGAGTCTCTAAAGTATAATAAAAGAAAAAGAAAAAGAGTCTGCCAATTTCACTTT C <u>TAGTTTCACCTTC</u> CCTTTTGAACGTGAGCTGAAGGAAACAAACAAAAAGAACAGAGGCCACTTGTATATATA GGTCTCTCAGCATTATTGGTGGCAGAAGAGGAAATTCTGAAGAGTGCAGCTGCCTGAACCGAGCCCTGCCG AACAGCTGAGAATTGCACTGCAACCATGAGGTAATATTTCCCTTCGTAT	chr10:91061551- 91061906
TAP2	TTCCCCCCGCACCAACTCACCAGCCGCGGGGGAGACCCGAGCTCCGGGACTTCTGCTTCAGCGTGAGG TCCGCTCCGTCTCTCCAACCTCGCTACCGGCTCTGGTCCGCCAGCTACGCTCGGCCAGGGCGGGCCTCAGGG CTCGGGCAGC <u>CTTTCGCTTC</u> CTTCCCAGCCAAGGCCCTTATTCTGGGCTGGGCCCGGGAGGGGGCGCGC GAGACCCGACAGCGGAAGTGGAGCCGAACTCTGGTTCGCACTGTACAGGCTGCAATGAGTCTCACTCGC CTTTAGTGGCGTTACTCTGGGATATAAACTGCAAAAATGTTTCTTTATCATTAAAGTAAATACAGT	chr6:32806409- 32806769
DDX60	CTCAGGACCGGTGGTGTCCAAGACCCGCGAGCTGCGCGCCCGCGGGGAGGGAGTGAACAGAGACCTAGC GCAGAGCCAGGTGGAAGTTCCAGGTTACCCAGACCTGGCCTAGGACTCGGCGCTCTGAGCCACCCGAGCCA GTCTTTTATGCATCCGGCGGGA <u>GTTTCGGTTTC</u> CTTTCTCCTCTCAGAAGCACTTAG <u>GTTTCAGTTTC</u> CTTTCAGCA CGAATTAGGCGAGGCATTTCTGTGAAAGTTTAGCATCCTTCCCTTCAATCAGAATCTTAAAGGGGAGCATGGC GAGACGTTAGTTAAAGGTGAAGTTACAATAGCTAGGAAGAACCAGTTCTGGTATT	chr4:169239779- 169240134

Supplementary References

- 1 Mathelier, A. *et al.* JASPAR 2016: a major expansion and update of the open-access database of transcription factor binding profiles. *Nucleic Acids Res* **44**, D110-115 (2016).
- 2 Casper, J. *et al.* The UCSC Genome Browser database: 2018 update. *Nucleic Acids Res* **46**, D762-D769 (2018).

Supplementary Table 9. The exact *p*-values for the statistical analysis in Figures 1-4.

Figure	Comparison	<i>p</i> -value
1a	<i>IRF1</i> vs. control	< 0.0001
1b	HAV RNA, <i>IRF1</i> #1 vs. control	0.0002
1b	HAV RNA, <i>IRF1</i> #2 vs. control	0.0002
1b	HAV RNA, <i>RELA</i> #1 vs. control	0.015
1b	HAV titer, <i>IRF1</i> #1 vs. control	0.0091
1b	HAV titer, <i>IRF1</i> #2 vs. control	< 0.0001
1c	Fecal HAV RNA, <i>Irf1</i> ^{-/-} vs. WT	0.1304
1c	Liver HAV RNA (d7), <i>Irf1</i> ^{-/-} vs. WT	0.0286
1d	<i>IRF1</i> #2 vs. control	< 0.0001
1e	<i>IRF1</i> #2 vs. control	0.001
1f	Ruxolitinib vs. DMSO	0.0018
1f	Pyridone 6 vs. DMSO	0.0105
1f	DMSO-treated, <i>IRF1</i> #1 vs. control	0.0082
1f	DMSO-treated, <i>IRF1</i> #2 vs. control	0.0042
1f	Ruxolitinib-treated, <i>IRF1</i> #1 vs. control	0.0287
1f	Ruxolitinib-treated, <i>IRF1</i> #2 vs. control	< 0.0001
1g	Control sgRNA, <i>IRF1</i> #2 vs. control	0.0052
1g	<i>MAVS</i> sgRNA, <i>IRF1</i> #2 vs. control	0.0095
1g	<i>IRF3</i> sgRNA, <i>IRF1</i> #2 vs. control	0.0016
1h	<i>IRF1</i> #1 vs. control	0.0006
1h	<i>IRF1</i> #2 vs. control	0.0003
1h	DAA vs. control	0.0056
1i	24 h, <i>IRF1</i> #1 vs. control	< 0.0001
1i	24 h, <i>IRF1</i> #2 vs. control	< 0.0001
1i	48 h, <i>IRF1</i> #1 vs. control	< 0.0001
1i	48 h, <i>IRF1</i> #2 vs. control	< 0.0001
1j	DENV-24 h, <i>IRF1</i> vs. control siRNA	< 0.0001
1j	DENV-48 h, <i>IRF1</i> vs. control siRNA	0.0006
1j	ZIKV-24 h, <i>IRF1</i> vs. control siRNA	0.0015
1j	ZIKV-48 h, <i>IRF1</i> vs. control siRNA	0.0348
2a	Mock, PRDIII-I activity, <i>IRF1</i> #1 vs. control	< 0.0001
2a	Mock, PRDIII-I activity, <i>IRF1</i> #2 vs. control	< 0.0001
2a	Mock, PRDIII-I activity, <i>IRF1</i> #1 vs. <i>IRF3</i>	< 0.0001
2a	Mock, PRDIII-I activity, <i>IRF1</i> #2 vs. <i>IRF3</i>	< 0.0001
2a	HAV, PRDIII-I activity, <i>IRF1</i> #1 vs. control	< 0.0001
2a	HAV, PRDIII-I activity, <i>IRF1</i> #2 vs. control	< 0.0001
2a	HAV, PRDIII-I activity, <i>IRF1</i> #1 vs. <i>IRF3</i>	< 0.0001
2a	HAV, PRDIII-I activity, <i>IRF1</i> #2 vs. <i>IRF3</i>	< 0.0001
2a	Mock, ISRE activity, <i>IRF1</i> #1 vs. control	< 0.0001
2a	Mock, ISRE activity, <i>IRF1</i> #2 vs. control	< 0.0001
2a	Mock, ISRE activity, <i>IRF1</i> #1 vs. <i>IRF3</i>	< 0.0001
2a	Mock, ISRE activity, <i>IRF1</i> #2 vs. <i>IRF3</i>	< 0.0001
2a	HAV, ISRE activity, <i>IRF1</i> #1 vs. control	< 0.0001
2a	HAV, ISRE activity, <i>IRF1</i> #2 vs. control	< 0.0001
2a	HAV, ISRE activity, <i>IRF1</i> #1 vs. <i>IRF3</i>	< 0.0001
2a	HAV, ISRE activity, <i>IRF1</i> #2 vs. <i>IRF3</i>	< 0.0001
2b	PRDIII-I activity, SeV vs. Mock	0.0116
2b	ISRE activity, SeV vs. Mock	< 0.0001
2c	Mock, PRDIII-I activity, <i>IRF1</i> #1 vs. control	< 0.0001
2c	Mock, PRDIII-I activity, <i>IRF1</i> #2 vs. control	0.0001
2c	SeV, PRDIII-I activity, <i>IRF1</i> #1 vs. control	< 0.0001
2c	SeV, PRDIII-I activity, <i>IRF1</i> #2 vs. control	0.0002
2c	Mock, ISRE activity, <i>IRF1</i> #1 vs. control	< 0.0001
2c	Mock, ISRE activity, <i>IRF1</i> #2 vs. control	< 0.0001
2c	SeV, ISRE activity, <i>IRF1</i> #1 vs. control	< 0.0001
2c	SeV, ISRE activity, <i>IRF1</i> #2 vs. control	< 0.0001
2e	DMSO, <i>IRF1</i> #1 vs. control	< 0.0001
2e	DMSO, <i>IRF1</i> #2 vs. control	0.006
2e	ActD, <i>IRF1</i> #1 vs. control	0.0013

2e	ActD, <i>IRF1</i> #2 vs. control	0.04
2f	DENV-DMSO, <i>IRF1</i> vs. control siRNA	0.018
2f	DENV-ActD, <i>IRF1</i> vs. control siRNA	0.021
2f	ZIKV-DMSO, <i>IRF1</i> vs. control siRNA	0.0003
2f	ZIKV-ActD, <i>IRF1</i> vs. control siRNA	0.015
3e	<i>RARRES3</i> vs. control siRNA	< 0.0001
3e	<i>APOL6</i> vs. control siRNA	0.0049
3e	<i>ERAP2</i> vs. control siRNA	< 0.0001
3e	<i>NMI</i> vs. control siRNA	0.0004
3e	<i>MX1</i> vs. control siRNA	0.0094
3f	<i>RARRES3</i> vs. control siRNA	0.0015
3f	<i>ERAP2</i> vs. control siRNA	0.0047
3f	<i>NMI</i> vs. control siRNA	0.0072
3f	<i>MX1</i> vs. control siRNA	0.0125
3f	All 4 genes vs. control siRNA	0.004
3g	<i>PSMB9</i> vs. control siRNA	< 0.0001
3g	<i>IFIT3</i> vs. control siRNA	0.0348
3g	<i>ERAP2</i> vs. control siRNA	0.0383
3g	<i>APOL1</i> vs. control siRNA	< 0.0001
3g	<i>MX1</i> vs. control siRNA	0.0003
3g	DAA vs. control siRNA	< 0.0001
3h	<i>PSMB9</i> vs. control siRNA	0.0047
3h	<i>APOL1</i> vs. control siRNA	0.0027
3h	<i>MX1</i> vs. control siRNA	0.015
3h	All 3 genes vs. control siRNA	0.0003
3i	<i>RARRES3</i> vs. control siRNA	0.0272
3i	<i>PSMB9</i> vs. control siRNA	0.0275
3i	<i>ERAP2</i> vs. control siRNA	0.0206
3i	<i>MX1</i> vs. control siRNA	0.0192
3j	<i>PSMB9</i> vs. control siRNA	0.0196
3j	<i>MX1</i> vs. control siRNA	0.0155
3j	All 2 genes vs. control siRNA	0.0026
3k	<i>RARRES3</i> vs. control siRNA	0.0015
3k	<i>PSMB9</i> vs. control siRNA	< 0.0001
3k	<i>ERAP2</i> vs. control siRNA	0.0058
3k	<i>APOL1</i> vs. control siRNA	0.0011
3k	<i>CFB</i> vs. control siRNA	0.0003
3k	<i>APOL3</i> vs. control siRNA	0.002
3k	<i>NMI</i> vs. control siRNA	0.0004
3k	<i>MX1</i> vs. control siRNA	< 0.0001
3k	<i>DDX60</i> vs. control siRNA	0.0149
3l	<i>PSMB9</i> vs. control siRNA	0.0015
3l	<i>MX1</i> vs. control siRNA	0.0014
3l	All 2 genes vs. control siRNA	0.0002
4a	PH5CH8/ <i>IRF1</i> sgRNA, <i>RARRES3</i> vs. Vector	< 0.0001
4a	PH5CH8/ <i>IRF1</i> sgRNA, C113S vs. Vector	0.0215
4a	Huh-7.5 cells, <i>RARRES3</i> vs. Vector	< 0.0001
4b	24 h, DMSO, <i>RARRES3</i> vs. Vector	< 0.0001
4c	HAV-Luc, <i>RARRES3</i> vs. Vector	< 0.0001
4d	<i>RARRES3</i> vs. Vector	< 0.0001
4h	Rapamycin, HAV/NLuc vs. HCV/GLuc	< 0.0001
4h	Rapamycin, HAV/NLuc vs. DENV/NLuc	< 0.0001
4h	Torin1, HAV/NLuc vs. HCV/GLuc	< 0.0001
4h	Torin1, HAV/NLuc vs. DENV/NLuc	< 0.0001
4h	PI-103, HAV/NLuc vs. HCV/GLuc	0.003
4h	PI-103, HAV/NLuc vs. DENV/NLuc	< 0.0001
4i	Rapamycin vs. DMSO	< 0.0001
4i	Torin1 vs. DMSO	< 0.0001
4i	PI-103 vs. DMSO	< 0.0001