

Supplementary Materials for
Apolipoprotein E mediates cell resistance to influenza virus infection

Ping Gao *et al.*

Corresponding author: Jianwei Wang, jianwei.wang@ipbcams.ac.cn; George Fu Gao, gaof@im.ac.cn;
Fuping Zhang, zhangfp@im.ac.cn

Sci. Adv. **8**, eabm6668 (2022)
DOI: 10.1126/sciadv.abm6668

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Fig. S1

A

Screen	cells	Strain	Identical
Shapira 2009	HBEC	PR8	STAT1,IFITM2, OAS1,IRF9
Ward 2012	HBEC30	WSN	IFITM1, IFITM3, IRF9, CYLC1
Brass 2009	U2OS	PR8	IFITM3
Su 2013	A549	WSN	AXL
Karlas 2010	A549	WSN	IRF2

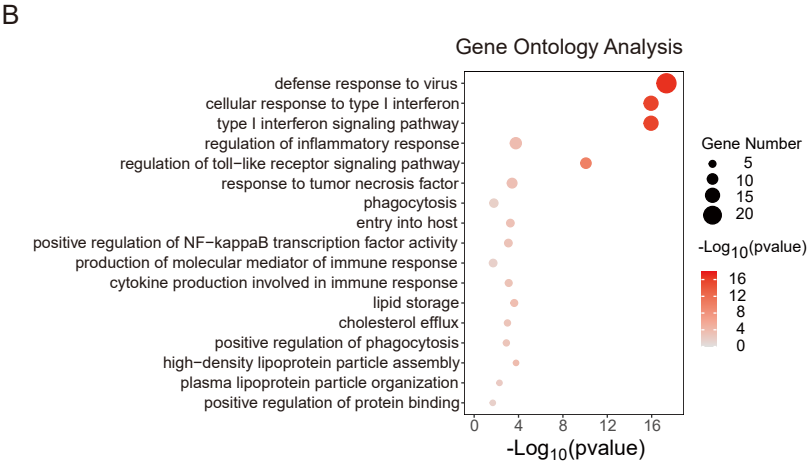


Fig.S1. Identification of APOE as a factor that anti-IAV infection.
 (A) A comparison of genes identified in our screen with those obtained in other 5 published influenza genome-wide screens (miRNAs excluded).
 (B) Enriched biological processes identified by Gene ontology analysis (miRNAs excluded).

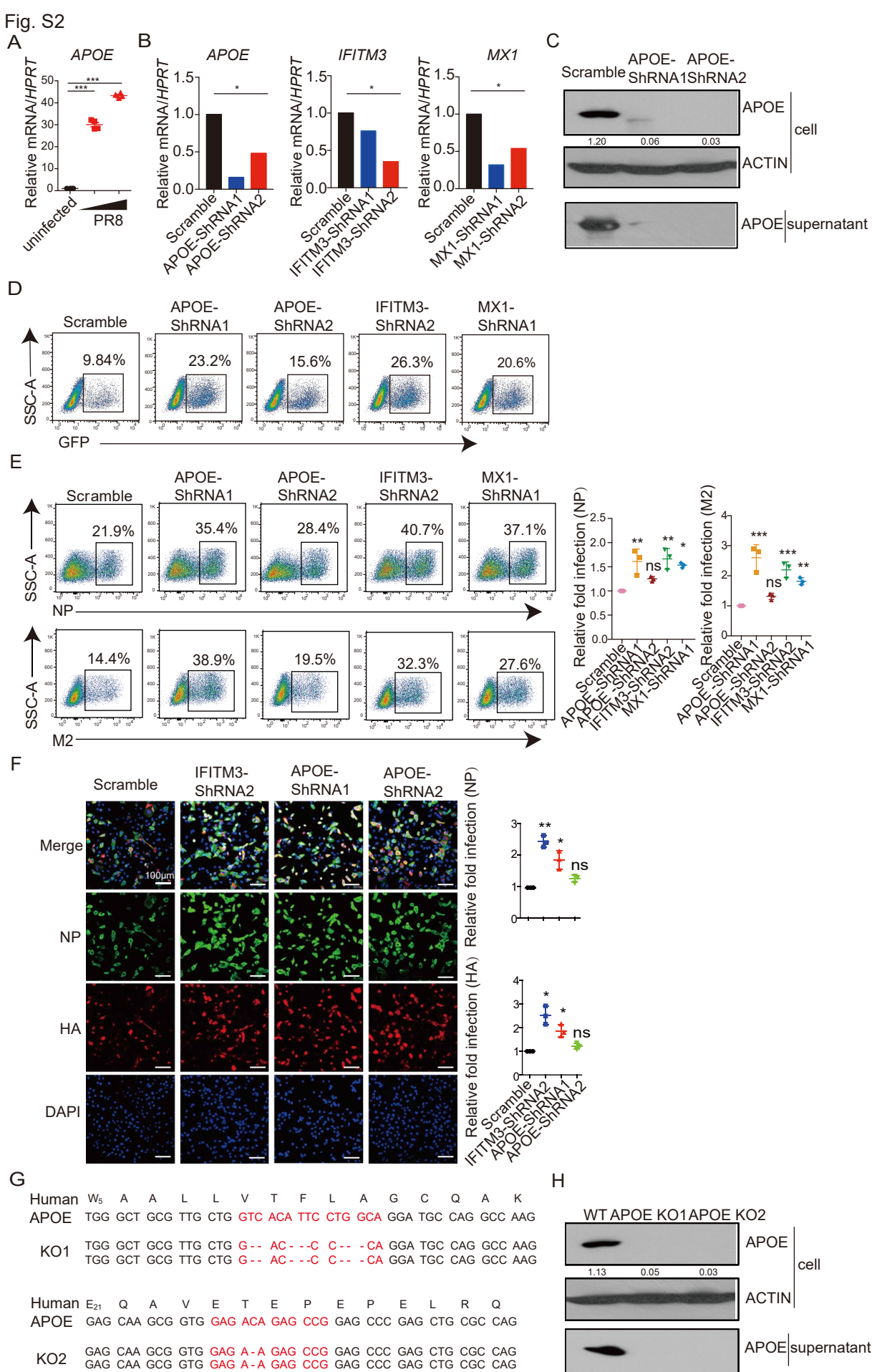


Fig. S2 Validation of APOE as a factor that anti-IAV infection in A549 cells.
 (A) APOE expression in A549 cells was detected by qRT-PCR 12 hrs after PR8 infection. Data are shown as mean±SD from at least three independent experiments.
 (B-C) Verification of APOE, IFITM3, MX1 gene knockdown efficiency by qRT-PCR (B) and western blot (C) in A549 cells. (D) A549 cells transduced with scramble shRNA or indicated gene shRNA were infected with PR8/NS1-GFP virus at MOI=0.3. GFP+ cells were assessed by flow cytometry 8 hrs after infection. The data presented are representative of at least three independent experiments. (E-F) A549 cells transduced with scramble shRNA or indicated gene shRNA were infected with PR8 at MOI=0.5. NP+ and M2+ cells were assessed by flow cytometry (E) or immunofluorescence microscopy (F) 12h after infection (left), relative fold infection normalized to non-targeting control from three independent experiments with standard deviation was statistically analyzed (right). Scale bar, 100µm. (G-H) APOE KO efficiency in A549 cells was analyzed by DNA sequencing (G) and western blot (H). P values were determined using Student's t-test. *P < 0.05, **P < 0.01, ***P < 0.001.

Fig. S3

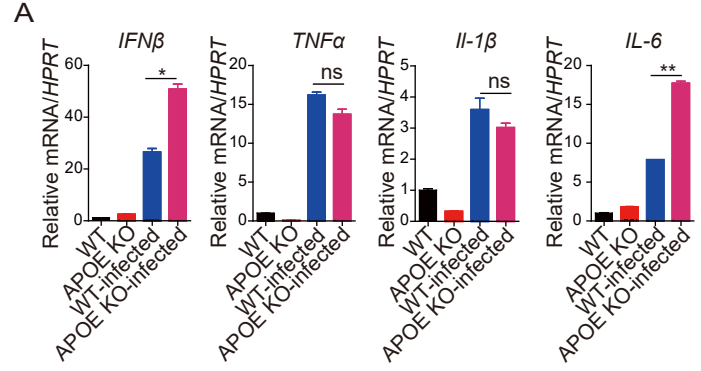


Fig. S3 Cytokine expression in WT and APOE KO A549 cells infected with PR8.
(A) A549 WT and APOE KO cells were infected with PR8 at MOI=0.5 or not. The indicated cytokine expression was determined by qRT-PCR and normalized to housekeeping gene *HPRT*. P values were determined using two-way ANOVA followed by Bonferroni post hoc test. ns, not significant, *P < 0.05, **P < 0.01.

Fig. S4

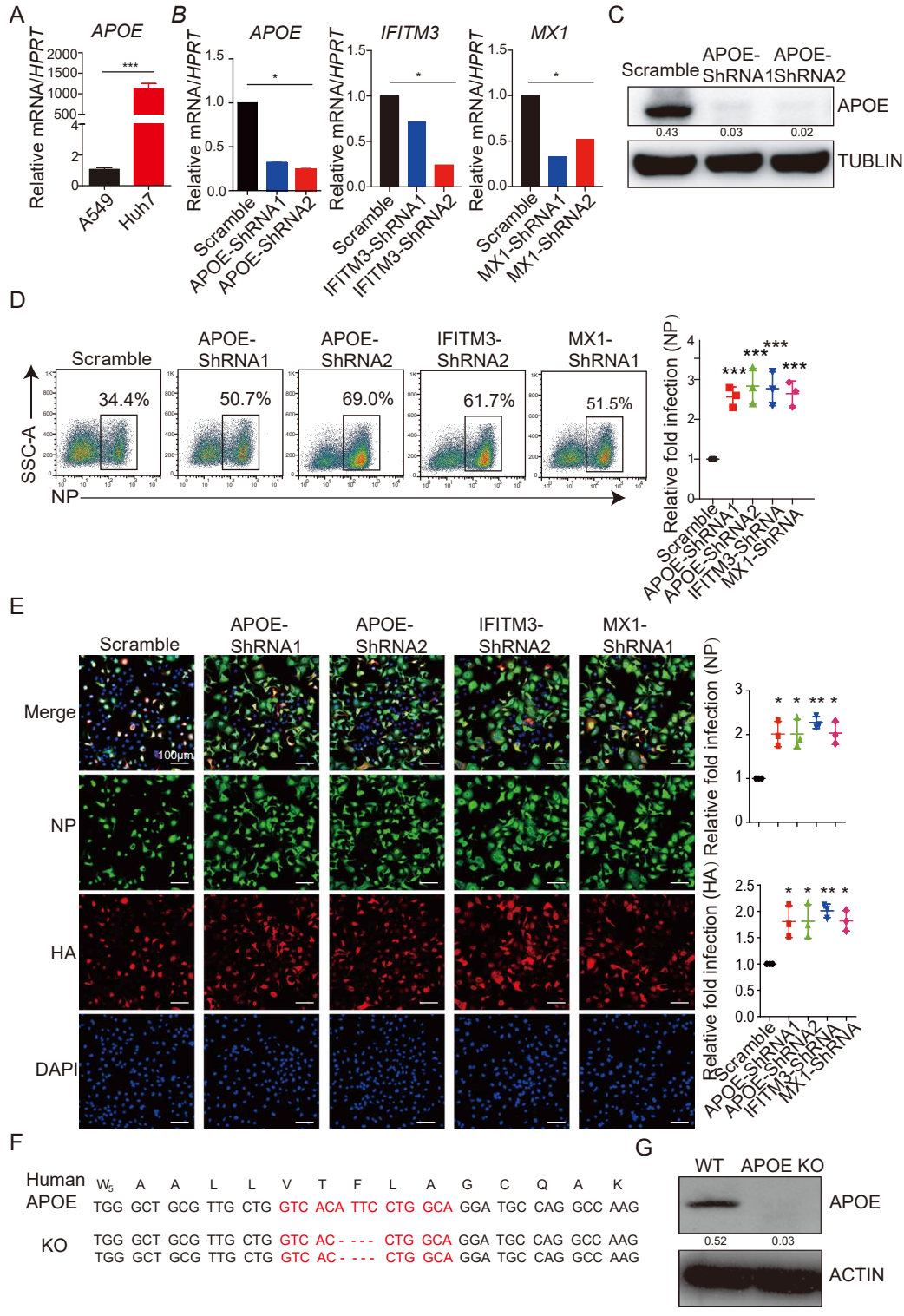


Fig. S4 Validation of APOE as a factor that anti-IAV infection in Huh7 cells.
 (A) APOE expression in A549 and Huh7 cells was detected by qRT-PCR. (B-C) The knock-down efficiency of APOE, IFITM3, and MX1 in Huh7 cells was analyzed by qRT-PCR (B) and western blot (C). (D-E) Huh7 cells transduced with scramble shRNA or indicated gene shRNA were infected with PR8 at MOI=0.3. NP+ cells were assessed by flow cytometry (D) or immunofluorescence microscopy (E) 12h after infection (left), relative fold infection normalized to non-targeting control from three independent experiments with standard deviation was statistically analyzed (right). Scale bar, 100µm. (F-G) APOE KO efficiency in Huh7 cells was confirmed by DNA sequencing (F) and western blot (G). P values were determined using Student's t-test. *P < 0.05, **P < 0.01, ***P < 0.001.

Fig. S5

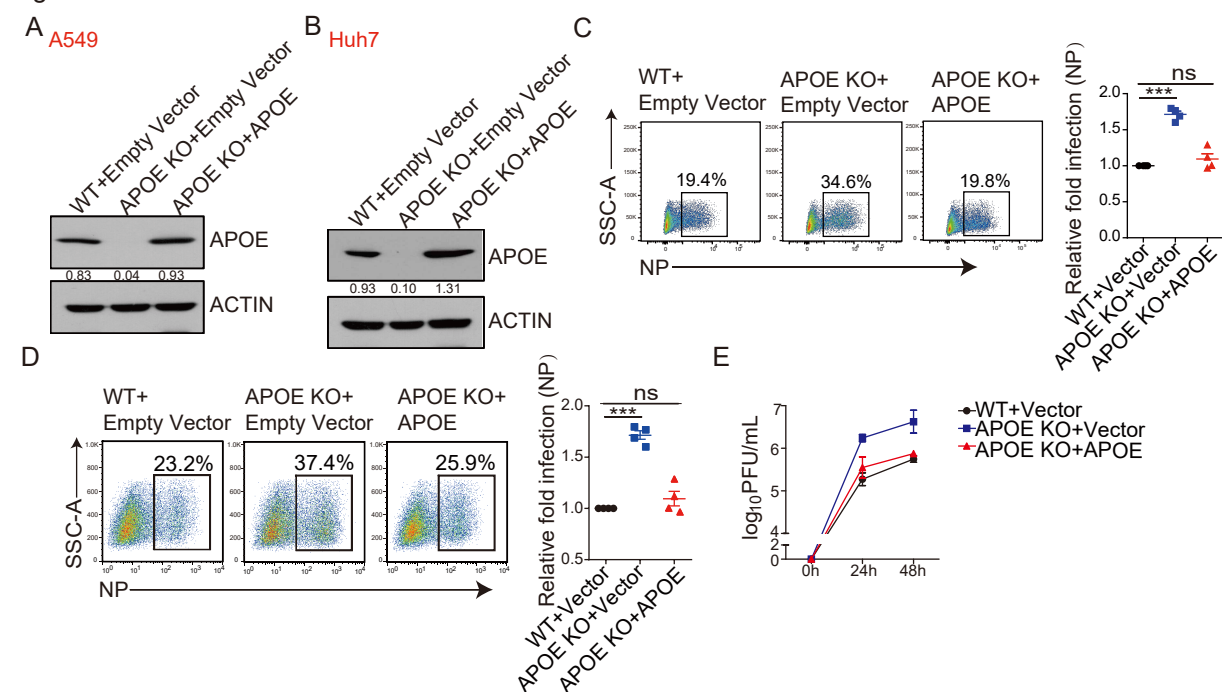


Fig. S5 Overexpression APOE in APOE KO cells protect the cells from virus infection. (A-B) APOE expression in APOE KO+APOE A549 cells (A) or Huh7 cells (B). The data presented are representative of at least three independent experiments. (C-D) A549 (C) and Huh7 (D) cells stably transduced with APOE or empty vector were infected with PR8 and NP+ cells were assessed 12 hrs after viral infection by flow cytometry (left). Relative fold infection from four independent experiments with standard deviation was statistically analyzed (right). (E) A549 cells as in (C) were infected with PR8 with low MOI=0.01, supernatant was collected to detect the virus titer by plaque assay. Data with mean \pm SD from three independent experiments was statistically analyzed. P values were determined using one-way ANOVA followed by Tukey's multiple-comparisons test. *P < 0.05, **P < 0.01, ***P < 0.001.

Fig. S6

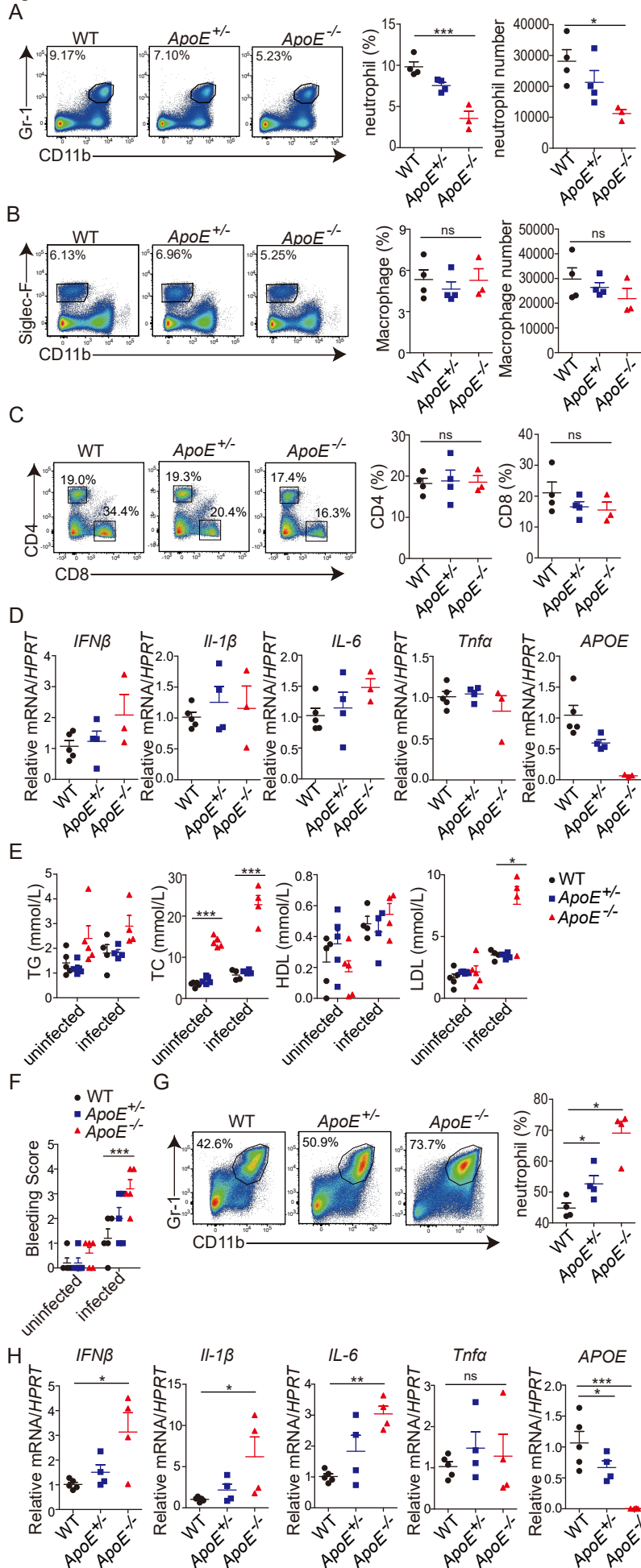


Fig. S6 The increased inflammation in the APOE deficient mice infected with PR8.
 (A-C) The percentage and cell number of Neutrophil (A), Alveolar macrophage (B), CD4 and CD8 cells (C) in the lung of uninfected WT, *ApoE*^{+/-} and *ApoE*^{-/-} mice was analyzed by flow cytometry. Each dot represents data from one mouse.
 (D) Cytokine expression in the lung of uninfected WT, *ApoE*^{+/-} and *ApoE*^{-/-} mice was detected by qRT-PCR. Each dot represents data from one mouse. (E) Triglycerideon (TG), cholesterol (TC), high-density lipoprotein (HDL), and low density lipoprotein (LDL) in serum of WT, *ApoE*^{+/-} and *ApoE*^{-/-} mice at baseline and 4 days after infection. Each dot represents data from one mouse. (F) Severity of bleeding was scored quantitatively from n = 5 mice per group. (G) WT, *ApoE*^{+/-} and *ApoE*^{-/-} mice were infected with 1000 pfu PR8, neutrophil infiltration of the lung at day 4 post infection were analysed by flow cytometry. (H) Cytokines and *APOE* expression in WT, *ApoE*^{+/-} and *ApoE*^{-/-} lungs at day 4 post infection were detected by qRT-PCR. Each dot represents data from one mouse. P values were determined using one-way ANOVA followed by Tukey's multiple-comparisons test. *P < 0.05, **P < 0.01, ***P < 0.001.

Fig. S7

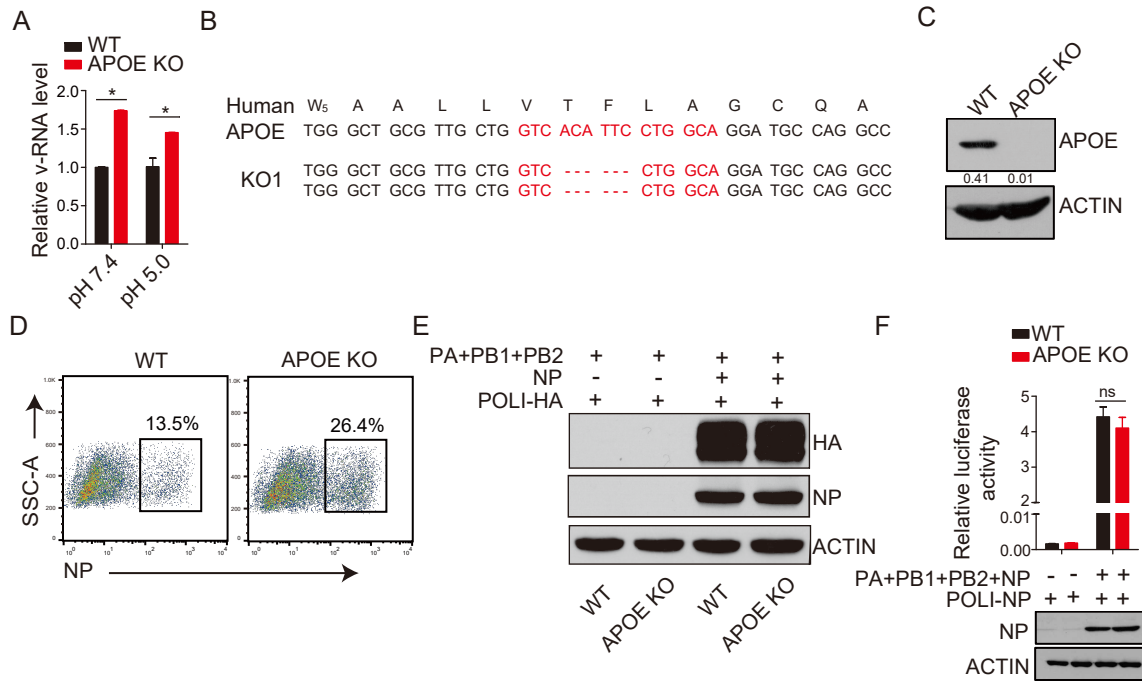


Fig. S7 APOE deficiency affects viral entry but not RNA synthesis.

(A) Viral fusion of WT and APOE KO A549 cells was analyzed by acid bypass assay. The relative v-RNA level from three independent experiments with standard deviation was statistically analyzed. (B-C) APOE KO efficiency in HEK293 cells was confirmed by DNA sequencing (B) and immunoblot (C). (D) NP+ cells in HEK293 WT and APOE KO cells were analyzed 12hrs after PR8 infection by flow cytometry. Data are representative of three independent experiments. (E) HEK293 WT and APOE KO cells were transfected with a POLI-driven RNA expression plasmid encoding the HA v-RNA segment and RNP expression plasmids pcDNA3.1-PB2, pcDNA3.1-PB1, pcDNA3.1-PA, and pcDNA3.1-NP. NP and HA were detected by western blot at 24 hrs post transfection. Data are representative of three independent experiments. (F) HEK293 WT and APOE KO cells were transfected with the luciferase reporter plasmid pPoNP-Luc and the internal control plasmid Renilla together with the plasmids pcDNA3.1-PB2, pcDNA3.1-PB1, pcDNA3.1-PA, and pcDNA3.1-NP. Cell lysates were analyzed 36 h after transfection to measure firefly and Renilla luciferase activities. Expression of NP and ACTIN was detected by immunoblot Blot. Data are representative of three independent experiments. P values were determined using two-way ANOVA followed by Bonferroni post hoc test. *P < 0.05, **P < 0.01, ***P < 0.001.

Fig. S8

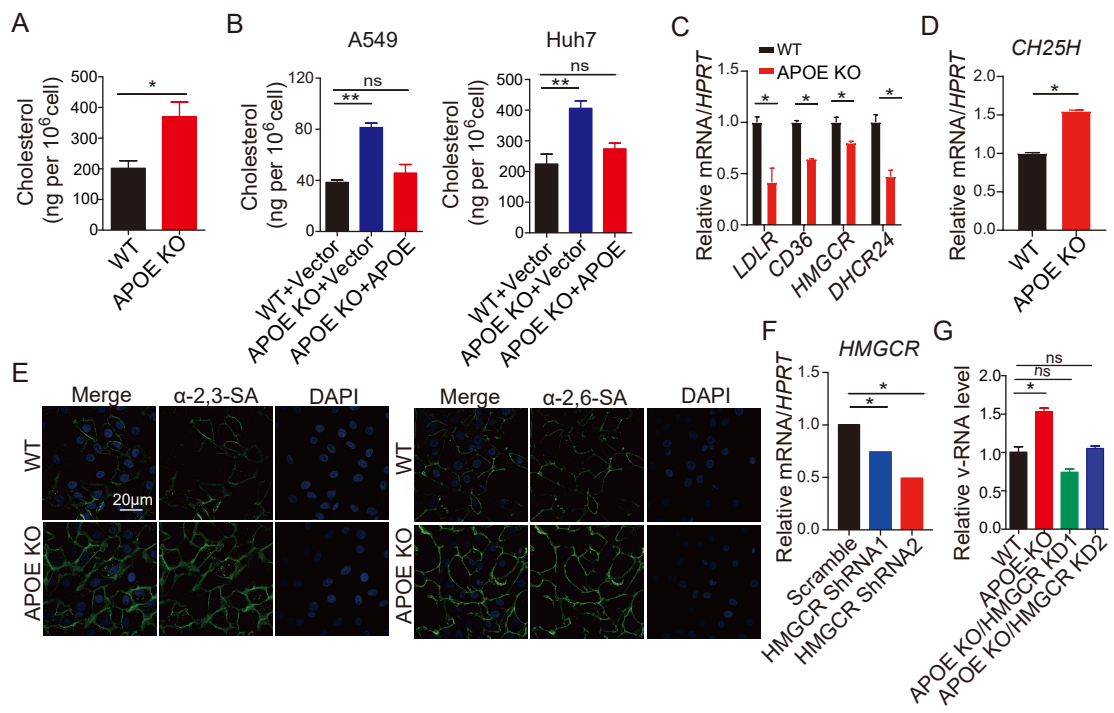


Fig. S8 APOE KO impacts cell cholesterol homeostasis.

(A) Total cellular cholesterol in WT or APOE KO Huh7 cells was detected by Amplex Red Cholesterol assay. Data are shown as mean±SD from at least three independent experiments. (B) Total cellular cholesterol in WT+Empty vector, APOE KO+Empty vector, and APOE KO+APOE cells was detected as in (A). Data are shown as mean±SD from at least three independent experiments. (C-D) Genes associated with cholesterol homeostasis (C) and *CH25H* (D) were detected by qRT-PCR in A549 WT and APOE KO cells. Data are shown as mean±SD from at least three independent experiments. (E) A549 WT and APOE KO cells were stained with α-2,3-linked SA or α-2,6-linked SA and detected by confocal microscopy, the low magnification microscopic images were shown here. Scale bar, 20 μm. (F) Knockdown efficiency of *HMGCR* in A549 cells was analyzed by qRT-PCR. Data are shown as mean±SD from at least three independent experiments. (G) Virus attachment in WT, APOE KO, and APOE KO/*HMGCR* KD cells was determined by qRT-PCR. The relative v-RNA level from three independent experiments with standard deviation was statistically analyzed. P values were determined using one-way ANOVA followed by Tukey's multiple-comparisons test. *P < 0.05, **P < 0.01, ***P < 0.001.

Fig. S9

A

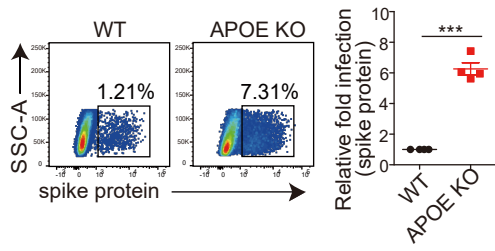


Fig.S9. APOE Inhibits SARS-CoV-2 Infection.

(A) Huh7 WT and APOE KO cells infected by SARS-CoV-2 at MOI=0.1 were collected 36hrs after infection and analyzed for spike protein-positive cells by flow cytometry (left), and relative fold infection from four independent experiments with standard deviation was statistically analyzed (right).

Supplementary Table 1

	log2FoldChange	pvalue
ACTC1	-1.797552593	0.000570226
ACYP1	1.554569599	0.000872372
AKIP1	1.594915054	0.000647535
ALYREF	1.872154022	0.000537387
Amn1	2.115297227	0.000116869
APOA1	6.284104918	6.70E-132
APOE	5.718443798	1.51E-97
APPL2	-3.450038548	3.92E-10
ARL8B	1.695902801	3.49E-05
ATP4B	1.57239887	0.000487702
AXL	3.461125432	1.96E-29
BCI10	2.981569753	5.29E-19
BDP1	-1.540731063	0.000947324
BIRC3	2.772089825	4.89E-23
BPIFB1	2.718087768	4.57E-21
C10orf10	-2.343643835	7.17E-07
C11orf21	-1.77915884	0.000374837
C19orf59	1.643878779	0.000133049
C1orf105	1.474711914	0.000337742
C2orf44	1.475430362	0.000892304
C8orf22	1.956746325	0.000280107
CARD10	-2.150679206	0.000486586
CARD14	-2.248769033	0.012098155
CASP10	2.976705147	6.32E-12
CCDC70	1.886043794	4.54E-05
CENPN	1.513901598	7.95E-05
CENPV	-2.934925097	3.67E-05
CGA	1.778969735	3.38E-06
CHCHD1	-1.924941268	0.001152745
CHD4	1.656365571	0.001012869
CPLX2	1.736979425	0.000730312
CPNE4	1.667597511	6.77E-05
CST5	-1.604932698	4.50E-05
CTDP1	1.694416322	0.000335591
CX3CL1	3.40969897	2.68E-25
CYB5R2	1.748793546	3.96E-07
CYBA	3.232616689	5.43E-25
CYLC1	1.820589141	6.18E-06
CYP2C9	-1.645351821	0.000489519
DCTD	1.949684345	0.000659782
DDX51	-2.065656768	0.0007546
DEFB129	-1.69205116	0.001111124
DIO3	1.688933337	0.000493911
DPH5	1.353933115	0.00057607
DYRK1B	1.476473935	0.000643555
ERAL1	-1.730214682	0.00025842
FAM170A	-1.794948274	0.001139334
FBLN2	1.5330161	0.000438793
FOCAD	1.428918663	0.000579582
GPR89A	1.575906373	0.000363514
GPR98	1.632730874	0.000271307
GZMA	1.48494826	7.48E-05
HFE	1.587833845	3.86E-05
HMGN4	1.447276064	0.000882586
hsa-let-7a-2	2.830615943	9.67E-08
hsa-let-7a-3	2.42867971	8.98E-05

hsa-let-7b	2.425355645	7.83E-05
hsa-let-7f-1	3.065251664	5.80E-10
hsa-let-7f-2	2.008455961	0.000520619
hsa-mir-101-2	2.236830964	3.60E-07
hsa-mir-103a-1	1.871434321	0.000122189
hsa-mir-103a-2	1.948784472	1.44E-06
hsa-mir-103b-2	1.948784472	1.44E-06
hsa-mir-105-1	2.545550076	6.11E-05
hsa-mir-10b	2.983285475	2.77E-08
hsa-mir-1-1	1.98232726	4.42E-05
hsa-mir-1182	2.135958418	1.43E-06
hsa-mir-1-2	2.222339609	0.000183479
hsa-mir-1204	1.686180005	0.000454321
hsa-mir-124-1	2.070117963	9.07E-05
hsa-mir-124-3	1.977818351	4.21E-05
hsa-mir-1244-2	1.678511635	0.000217186
hsa-mir-1250	2.506162764	1.15E-05
hsa-mir-1253	1.982528211	1.78E-05
hsa-mir-1255b-1	2.761009949	0.000610677
hsa-mir-125a	2.421995533	3.84E-06
hsa-mir-1262	2.281538802	4.57E-08
hsa-mir-1265	1.780958972	2.71E-05
hsa-mir-1267	2.172433474	0.000191632
hsa-mir-1268b	2.141692984	0.000350255
hsa-mir-1269a	2.000917803	0.000331606
hsa-mir-127	2.301899525	5.08E-05
hsa-mir-1270-1	1.435139948	0.000353742
hsa-mir-1270-2	1.435139948	0.000353742
hsa-mir-1273g	2.038201901	2.96E-05
hsa-mir-1276	2.147365316	9.96E-05
hsa-mir-1283-1	2.2060638	0.000101849
hsa-mir-1285-2	1.973287292	7.87E-05
hsa-mir-1286	2.217421681	0.000178334
hsa-mir-1287	2.488109131	4.24E-07
hsa-mir-1290	2.692135215	1.07E-06
hsa-mir-1294	1.877438711	2.62E-05
hsa-mir-1295a	1.675332553	4.27E-05
hsa-mir-1295b	1.675332553	4.27E-05
hsa-mir-1299	2.356521753	1.78E-05
hsa-mir-1302-1	2.373938617	0.000287608
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hsa-mir-1302-11	1.644360976	1.00E-05
hsa-mir-1302-2	1.644360976	1.00E-05
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hsa-mir-3926-2	1.600303332	4.72E-05
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hsa-mir-4258	1.944510442	7.41E-05
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hsa-mir-4265	2.128169599	2.37E-05
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hsa-mir-4278	2.020500134	7.50E-05
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hsa-mir-4298	2.341744927	3.54E-07
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hsa-mir-4327	1.927869031	0.000974728
hsa-mir-4328	1.614147154	0.001089243
hsa-mir-4422	2.818096024	2.95E-06
hsa-mir-4431	2.636765004	1.50E-07
hsa-mir-4435-1	2.173326851	0.000557726

hsa-mir-4435-2	2.772323207	1.55E-07
hsa-mir-4436b-1	2.249723748	0.000237772
hsa-mir-4438	1.874264763	0.000667947
hsa-mir-4444-1	1.988429301	8.02E-06
hsa-mir-4444-2	1.988429301	8.02E-06
hsa-mir-4456	2.716379703	6.84E-08
hsa-mir-4462	2.482405039	1.77E-05
hsa-mir-4465	1.880051149	0.000425154
hsa-mir-4467	2.95251586	3.65E-05
hsa-mir-4470	2.075647405	5.71E-05
hsa-mir-4496	2.076356477	1.44E-05
hsa-mir-449a	1.895065986	0.000475069
hsa-mir-4500	2.459952241	1.43E-06
hsa-mir-4514	3.304397796	2.04E-08
hsa-mir-4518	3.046018056	3.07E-08
hsa-mir-451a	1.704373047	9.12E-05
hsa-mir-451b	1.704373047	9.12E-05
hsa-mir-452	2.090680596	0.000483894
hsa-mir-4522	2.569931586	2.27E-07
hsa-mir-4531	3.920034912	3.45E-08
hsa-mir-4537	2.501469024	5.82E-07
hsa-mir-4634	2.605866941	8.63E-05
hsa-mir-4635	1.951773897	4.72E-05
hsa-mir-4650-1	1.929022319	0.00058158
hsa-mir-4654	2.140631035	2.00E-05
hsa-mir-4656	1.835119255	0.000256873
hsa-mir-4662a	1.724404721	0.000136226
hsa-mir-4662b	2.11860719	9.36E-05
hsa-mir-4663	2.40414997	3.06E-05
hsa-mir-4665	2.644168978	6.70E-05
hsa-mir-4675	2.226185828	0.000206709
hsa-mir-4684	1.81925599	0.000486133
hsa-mir-4687	2.197233961	5.39E-05
hsa-mir-4693	2.919268707	2.00E-06
hsa-mir-4700	1.811655653	0.000122131
hsa-mir-4705	1.81407405	0.000209241
hsa-mir-4706	2.562903304	0.000520492
hsa-mir-4709	2.085961824	5.78E-05
hsa-mir-4713	1.804475094	0.00083318
hsa-mir-4715	2.078405618	0.000347845
hsa-mir-4723	1.909506997	8.33E-06
hsa-mir-4730	1.663529011	0.001214524
hsa-mir-4732	2.732115844	9.29E-05
hsa-mir-4736	3.639217617	2.96E-08
hsa-mir-4737	1.865659322	3.61E-05
hsa-mir-4738	1.864137888	0.000501399
hsa-mir-4742	2.068231976	2.58E-06
hsa-mir-4747	3.093604832	0.00019369
hsa-mir-4762	2.408753148	2.09E-06
hsa-mir-4764	2.104306915	1.44E-05
hsa-mir-4767	2.049474528	0.000457446
hsa-mir-4768	2.484502921	3.72E-08
hsa-mir-4771-1	1.798309681	0.000125037
hsa-mir-4773-1	2.022802579	0.000283058
hsa-mir-4773-2	2.022802579	0.000283058
hsa-mir-4774	2.244741558	0.000663409
hsa-mir-4777	2.261496688	0.000183443
hsa-mir-4786	2.424387479	0.000133422

hsa-mir-4791	2.482083414	6.31E-05
hsa-mir-4796	1.75492192	0.000147969
hsa-mir-4798	1.569336063	0.000761796
hsa-mir-488	2.181577453	7.92E-05
hsa-mir-489	2.236218943	0.000165308
hsa-mir-492	2.963350504	2.62E-07
hsa-mir-499a	2.040899432	9.44E-07
hsa-mir-5003	1.774897979	0.000941288
hsa-mir-5004	2.930691848	3.50E-08
hsa-mir-500b	1.859832814	0.001012424
hsa-mir-5011	1.744009375	0.000148942
hsa-mir-503	2.292401361	5.32E-09
hsa-mir-505	2.162785721	0.000364248
hsa-mir-506	1.840373878	0.000364144
hsa-mir-5089	3.172551724	0.000700467
hsa-mir-509-1	1.529913581	0.000845571
hsa-mir-509-2	1.529913581	0.000845571
hsa-mir-5094	2.084663204	0.000159657
hsa-mir-512-1	1.732179873	5.75E-06
hsa-mir-512-2	1.732179873	5.75E-06
hsa-mir-515-1	1.997925826	2.70E-07
hsa-mir-515-2	1.997925826	2.70E-07
hsa-mir-516b-2	1.666579062	0.000365229
hsa-mir-517a	1.542844698	0.001164207
hsa-mir-5189	1.84581678	0.001207206
hsa-mir-518b	1.903189896	0.000800879
hsa-mir-5197	1.831856497	0.000202646
hsa-mir-519d	1.95468492	0.000184993
hsa-mir-519e	1.775548927	0.000473696
hsa-mir-520b	1.691207347	0.000118302
hsa-mir-520f	1.648968719	0.000789795
hsa-mir-520g	1.618790335	4.70E-05
hsa-mir-520h	1.489841803	0.000224604
hsa-mir-525	1.83513457	0.000773593
hsa-mir-526a-1	1.88452407	6.62E-05
hsa-mir-526a-2	1.718425568	6.52E-05
hsa-mir-548a-2	2.308975498	9.63E-07
hsa-mir-548ae-2	2.262627482	1.43E-05
hsa-mir-548ag-1	2.065228627	0.000165001
hsa-mir-548ap	1.949100294	1.11E-07
hsa-mir-548at	1.892439961	0.001039859
hsa-mir-548au	2.528103256	3.21E-05
hsa-mir-548av	2.014710375	0.000347169
hsa-mir-548aw	2.203112799	8.73E-05
hsa-mir-548az	2.821424247	8.41E-07
hsa-mir-548c	1.849708266	1.86E-07
hsa-mir-548n	1.926201819	8.21E-05
hsa-mir-548s	2.621209971	4.56E-10
hsa-mir-548t	1.611128141	0.000779127
hsa-mir-548v	3.129901019	9.16E-05
hsa-mir-548w	1.950761827	1.06E-05
hsa-mir-548y	2.197061701	9.55E-05
hsa-mir-548z	1.849708266	1.86E-07
hsa-mir-550a-1	1.640914859	1.10E-06
hsa-mir-550a-2	1.50573184	4.90E-05
hsa-mir-550b-1	1.640914859	1.10E-06
hsa-mir-550b-2	1.50573184	4.90E-05
hsa-mir-551a	2.127221182	0.000547767

hsa-mir-556	2.993638191	6.13E-08
hsa-mir-5572	2.306016	2.17E-06
hsa-mir-5579	2.186014112	0.000928432
hsa-mir-5584	2.269197705	1.95E-08
hsa-mir-5587	2.278196484	0.000384245
hsa-mir-5680	2.270316928	2.43E-05
hsa-mir-5683	1.867271909	0.000670168
hsa-mir-5684	2.405476164	2.07E-06
hsa-mir-5688	1.754589847	0.000829096
hsa-mir-5691	2.038341515	6.17E-05
hsa-mir-5692c-1	2.389999811	0.000671696
hsa-mir-5694	2.289432876	2.59E-06
hsa-mir-5695	2.431858009	2.19E-05
hsa-mir-5696	2.107330486	1.73E-05
hsa-mir-5697	2.060649325	4.39E-05
hsa-mir-5704	1.715046106	0.00049774
hsa-mir-575	2.434181039	0.000536822
hsa-mir-580	2.083640182	0.000195999
hsa-mir-583	1.889670694	0.000671224
hsa-mir-584	2.069179378	0.000571325
hsa-mir-585	2.135648888	0.00032423
hsa-mir-586	2.159285409	0.000292152
hsa-mir-587	1.935472276	0.000860231
hsa-mir-593	3.323148369	0.000586701
hsa-mir-597	1.979714745	9.44E-05
hsa-mir-603	1.985416015	0.00014169
hsa-mir-605	2.358360297	5.65E-06
hsa-mir-6071	2.277366019	2.79E-05
hsa-mir-6073	2.013945528	0.001041369
hsa-mir-6075	2.187544653	0.000414819
hsa-mir-6082	2.030838764	0.000489843
hsa-mir-6089-1	2.130856743	6.10E-06
hsa-mir-6089-2	2.130856743	6.10E-06
hsa-mir-609	2.081808053	2.74E-05
hsa-mir-615	3.048172663	1.23E-06
hsa-mir-6165	3.13969952	1.81E-07
hsa-mir-629	5.308619557	1.15E-06
hsa-mir-641	2.392624037	6.42E-05
hsa-mir-642a	1.446191213	0.000308557
hsa-mir-642b	1.498293321	0.000280801
hsa-mir-646	2.275104022	0.000246847
hsa-mir-647	1.698260946	0.000659646
hsa-mir-6501	2.876264831	0.000305385
hsa-mir-6503	2.769381677	0.000260761
hsa-mir-6504	2.721830244	1.20E-08
hsa-mir-6505	1.887851897	0.000232118
hsa-mir-6513	2.235217102	8.56E-05
hsa-mir-6514	2.275719293	3.06E-06
hsa-mir-6516	2.087574747	0.000748601
hsa-mir-652	2.304263569	2.72E-05
hsa-mir-653	2.227598461	0.000100116
hsa-mir-663a	2.856219349	3.08E-07
hsa-mir-664a	1.991087588	1.85E-05
hsa-mir-665	2.531661484	2.76E-06
hsa-mir-6717	2.05635005	0.000930379
hsa-mir-6718	2.393738388	1.14E-05
hsa-mir-6723	1.97736799	0.00017642
hsa-mir-6735	3.053325166	1.44E-07

hsa-mir-6751	1.885771746	0.001110045
hsa-mir-676	1.855521166	0.000640764
hsa-mir-6761	2.402607889	0.000515766
hsa-mir-6767	2.970445329	3.81E-09
hsa-mir-6769a	1.739748066	0.000985796
hsa-mir-6773	2.198422563	1.06E-06
hsa-mir-6776	3.495217128	1.19E-06
hsa-mir-6781	1.756403678	0.000782407
hsa-mir-6785	3.127668161	0.000152265
hsa-mir-6786	2.923955516	0.00024818
hsa-mir-6793	2.225851671	3.42E-05
hsa-mir-6807	2.574678479	0.000540933
hsa-mir-6808	1.917395711	0.000141641
hsa-mir-6821	3.601222095	3.87E-06
hsa-mir-6831	2.113002365	2.07E-05
hsa-mir-6837	2.403644926	2.00E-06
hsa-mir-6840	1.840469788	5.89E-05
hsa-mir-6843	2.471175265	5.13E-05
hsa-mir-6848	2.427075012	0.000429028
hsa-mir-6852	1.995420524	8.58E-05
hsa-mir-6853	2.158333672	0.001017968
hsa-mir-6864	1.98351533	0.001103709
hsa-mir-6874	1.885981164	0.00108663
hsa-mir-6886	2.123283326	0.000745974
hsa-mir-6889	2.22408091	1.36E-05
hsa-mir-6893	3.256515128	3.88E-09
hsa-mir-7113	2.362463541	9.48E-05
hsa-mir-7153	2.288815828	0.000506221
hsa-mir-7155	1.962283563	0.001007845
hsa-mir-7160	2.440647435	0.000170712
hsa-mir-762	2.120097057	1.84E-05
hsa-mir-764	1.961246844	4.92E-05
hsa-mir-7703	2.446347869	3.85E-05
hsa-mir-7854	1.920012561	0.000146854
hsa-mir-7973-1	1.713587637	4.14E-06
hsa-mir-7973-2	1.713587637	4.14E-06
hsa-mir-7975	2.227942146	3.98E-05
hsa-mir-8061	2.021166642	0.000161938
hsa-mir-8062	2.907060824	1.41E-09
hsa-mir-8064	3.0537755	3.25E-07
hsa-mir-8075	2.310386323	1.50E-06
hsa-mir-8085	2.26778685	0.000368463
hsa-mir-875	2.478719237	0.000382616
hsa-mir-887	1.841793708	0.000541667
hsa-mir-888	2.258840589	6.91E-05
hsa-mir-92a-1	2.330384535	6.87E-06
hsa-mir-92a-2	2.619610497	9.91E-09
hsa-mir-92b	2.584835851	0.000126768
hsa-mir-93	2.313381063	8.88E-05
hsa-mir-936	1.983530575	0.00057995
hsa-mir-941-1	1.958448749	2.23E-05
hsa-mir-941-2	1.72392785	2.69E-05
hsa-mir-941-3	1.72392785	2.69E-05
hsa-mir-941-4	1.72392785	2.69E-05
hsa-mir-98	2.510155579	0.000144878
IFIT3	3.31636857	5.91E-07
IFITM1	4.087462841	1.74E-05
IFITM2	2.652076697	1.15E-05

IFITM3	4.499838345	2.42E-51
IFNA1	2.306683164	8.24E-18
IFNA4	2.469085272	3.36E-05
IFNLR1	3.816692787	0.000243751
IGFN1	1.216839724	0.000469937
IKZF5	-1.679464892	0.000781248
IRF2	3.748679288	1.84E-33
IRF9	3.115477217	3.99E-14
JKAMP	1.70453094	5.76E-05
KAT6B	-1.592996596	0.001228788
KCNK2	2.214279581	1.75E-09
KIF3B	1.618581509	2.46E-05
LDHA	1.937029619	1.49E-07
LGALS9C	-1.490571604	0.00040653
LILRB1	-1.594165388	0.000177804
LOC100507003	1.656404272	0.000406413
LOC200726	-2.418618652	0.000379082
LRRC8A	-1.593816945	0.000599693
LY96	4.722881689	5.55E-29
MAGEF1	-2.103448328	0.000295851
MET	3.716128463	2.40E-153
MFSD1	1.362509195	0.001061633
MRPL30	-1.789286153	2.62E-06
MX1	4.667009572	2.84E-66
NEK5	2.25528567	0.000697987
NFKBIA	-2.073434651	4.66E-06
NFKBID	2.095206425	1.72E-15
NLRP6	-2.67025501	0.000219377
NLRP8	5.130222879	1.85E-55
NOL9	-1.728915709	0.000493413
NOTO	1.422795231	0.000205277
NR1H2	5.402826668	1.73E-16
NTN1	-2.003570247	2.38E-06
NUP62	-1.715644621	0.00013238
OAS1	5.491853096	1.04E-27
OAS2	6	2.10E-17
OAS3	4.485426827	8.67E-20
OR4F16	3.05137128	6.62E-178
OR4F21	3.05137128	6.62E-178
OR4F29	3.05137128	6.62E-178
OR4F3	3.05137128	6.62E-178
OR8H2	2.268337304	4.67E-13
PLCG1	-1.765946798	0.000658464
PLCZ1	1.834632496	0.000126962
PNPT1	3.557282956	1.09E-15
PTOV1	1.503928034	0.000986122
PTPN22	2.436784507	5.94E-19
PYGO1	1.813248274	2.90E-06
QTRTD1	-1.666046251	6.13E-05
RCSD1	2.334182221	2.90E-11
RELA	3.323736504	1.14E-08
RNASEH2A	1.43256484	0.000463371
RORC	1.491369542	1.02E-05
RPS4Y2	1.59183847	0.000153048
RUNX1T1	-1.682404707	0.00073392
SACM1L	1.66594539	1.81E-06
SERTAD4	-2.033350311	3.02E-05
SH3D21	-2.320255724	0.000574129

SIGLEC8	1.496879933	0.000841657
SLC2A8	-3.330059966	1.09E-07
SLC7A11	-1.803994971	0.00038486
SPEN	-2.242320892	4.46E-05
STAT1	4.531381461	7.60E-07
STAT2	4.107687869	9.20E-09
TAF1L	1.583200423	2.71E-05
TAP1	7.988684687	5.91E-08
TDO2	-1.911001838	0.000216932
THOP1	2.368376515	9.01E-19
TICAM1	-2.597895443	0.000218753
TINAG	-2.3743306	0.000574913
TLR10	2.974430861	3.51E-244
TLR5	-2.051023593	0.000260181
TMEM167A	-1.575694212	0.001197439
TMEM48	1.595752728	0.000368374
TNF	-2.446077067	5.42E-08
TOR4A	-2.672730078	0.000122461
TRAT1	1.907368774	3.56E-06
TRIM22	4.301477045	3.06E-34
TSHB	-2.012948484	0.000701476
TTYH2	1.656687794	0.000105852
UBQLN1	4.993841022	3.36E-47
VAX1	-1.741161563	0.000696302
VIP	-2.111718055	0.000151257
XAF1	3.839198232	4.31E-41
XIRP2	-2.32180315	0.000290226
ZBTB9	-1.716792135	0.000423235
ZDHHC1	-2.459644393	1.47E-05
ZDHHC2	-1.942785943	0.000226663
ZNF267	-2.09280184	0.000577893
ZNF43	-1.456487344	0.000528189
ZNF507	-1.940540362	0.001006836
ZNF664-FAM101A	1.416816859	0.001182165
ZSCAN25	-1.784811091	0.000948652

Supplementary Table 2 Primers used in this study

Primers used in two-step PCR for screening	
v2Adaptor_F	AATGGACTATCATATGCTTACCGTAACTTGAA AGTATTTTCG
v2Adaptor_R	TCTACTATTCTTTCCCCTGCACTGTTGTGGGC GATGTGCGCTCTG
Illumina F-01	AATGATACGGCGACCACCGAGATCTACACTCT TTCCCTACACGACGCTCTTCCGATCTTAAGTA GAGTCTTGTGGAAAGGACGAAACACCG
Illumina R-01	CAAGCAGAAGACGGCATAACGAGATAAGTAGA GGTGACTGGAGTTCAGACGTGTGCTCTTCCG ATCTTTCTACTATTCTTTCCCCTGCACTGT
Illumina F-02	AATGATACGGCGACCACCGAGATCTACACTCT TTCCCTACACGACGCTCTTCCGATCTATACAC GATCTCTTGTGGAAAGGACGAAACACCG
Illumina R-02	CAAGCAGAAGACGGCATAACGAGATACACGAT CGTGACTGGAGTTCAGACGTGTGCTCTTCCG ATCTATTCTACTATTCTTTCCCCTGCACTGT
qPCR primers used in this study	
IAV v-RNA-RT-F	ATTTGCCTATGAGACCGATGCT
IAV v-RNA-RT-R	AGGATGGGGGCTGTGACC
APOE-RT-H-F	AAGTCTGGGATCCTTGAGTCC
APOE-RT-H-R	AGGAATGTGACCAGCAACG
IAV M1 mRNA-RT-F	AAGACCAATCCTGTCACCTCTGA
IAV M1 mRNA-RT-R	CAAAGCGTCTACGCTGCAGTCC
IAV NP mRNA-RT-F	GATTGGTGGAAATTGGACGAT
IAV NP mRNA-RT-R	AGAGCACCATTCTCTCTATT
HMGCR-RT-H-F	GACGCAACCTTTATATCCGTTT

<i>HMGCR</i> -RT-H-R	TTGAAAGTGCTTTCTCTGTACCC
<i>LDLR</i> -RT-H-F	AGGTTGAAACGTTGCCTCAG
<i>LDLR</i> -RT-H-R	TCGTTTCTTTCGCATCTGTC
<i>CD36</i> -RT-H-F	TGGAACAGAGGCTGACAACCTT
<i>CD36</i> -RT-H-R	TTGATTTTGATAGATATGGGATGC
<i>DHCR24</i> -RT-H-F	CTACTACCACCGCCACACG
<i>DHCR24</i> -RT-H-R	GTTGTTGCCAAAGGGGATAA
<i>CH25H</i> -RT-H-F	CTTCGACATGGAGTTCTTCGT
<i>CH25H</i> -RT-H-R	TGTGGAAGGTGCGGTACA
<i>IFITM3</i> -RT-H-F	CGAAACTACTGGGGAAAGGGA
<i>IFITM3</i> -RT-H-R	ATTCATGGTGTCCAGCGAAGA
<i>MX1</i> -RT-H-F	GGTGGTGGTCCCCAGTAATG
<i>MX1</i> -RT-H-R	ACCACGTCCACAACCTTGTCT
Primers used for APOE overexpression	
<i>APOE</i> -F	AGTTAACCTCGAGGGATGAAGGTTCTGTGG
<i>APOE</i> -R	GACCAATTCGGCGCGTCAGTGATTGTCGCT

Supplementary Table 3 ShRNA sequence used in this study

<i>APOE</i> -ShRNA-1F	CCGGGACAATCACTGAACGCCGAAGCTCGAGCTTC GGCGTTCAGTGATTGTCTTTTTG
<i>APOE</i> -ShRNA-1R	AATTCAAAAAGACAATCACTGAACGCCGAAGCTCGA GCTTCGGCGTTCAGTGATTGTC
<i>APOE</i> -ShRNA-2F	CCGGACGAGACCATGAAGGAGTTGACTCGAGTCAA CTCCTTCATGGTCTCGTTTTTTG
<i>APOE</i> -ShRNA-2R	AATTCAAAAACGAGACCATGAAGGAGTTGACTCGA GTCAACTCCTTCATGGTCTCGT
<i>HMGCR</i> -ShRNA-1F	CCGGCCCTCGATGCTCTTGTGAATCTCGAGATTCA ACAAGAGCATCGAGGGTTTTTG

<i>HMGCR</i> -ShRNA-1R	AATTCAAAAACCCTCGATGCTCTTGTTGAATCTCGA GATTCAACAAGAGCATCGAGGG
<i>HMGCR</i> -ShRNA-2F	CCGGCCTGTATATTTACTTCCAGTTCTCGAGAACTG GAAGTAAATATACAGGTTTTTG
<i>HMGCR</i> -ShRNA-2R	AATTCAAAAACCTGTATATTTACTTCCAGTTCTCGAG AACTGGAAGTAAATATACAGG
<i>IFITM3</i> -ShRNA-1F	CCGGCCTGTTCAACACCCTCTTCATCTCGAGATGAA GAGGGTGTTGAACAGGTTTTTG
<i>IFITM3</i> -ShRNA-1R	AATTCAAAAACCTGTTCAACACCCTCTTCATCTCGA GATGAAGAGGGTGTTGAACAGG
<i>IFITM3</i> -ShRNA-2F	CCGGGCTTCATAGCATTTCGCCTACTCTCGAGAGTA GGCGAATGCTATGAAGCTTTTTG
<i>IFITM3</i> -ShRNA-2R	AATTCAAAAAGCTTCATAGCATTTCGCCTACTCTCGA GAGTAGGCGAATGCTATGAAGC
<i>MX1</i> -ShRNA-1F	CCGGCCTCTATTACTGAATGGAGATCTCGAGATCTC CATTCAAGTAATAGAGGTTTTTG
<i>MX1</i> -ShRNA-1R	AATTCAAAAACCTCTATTACTGAATGGAGATCTCGA GATCTCCATTCAAGTAATAGAGG
<i>MX1</i> -ShRNA-2F	CCGGCCACAAATGGAGTACAATAATCTCGAGATTAT TGTAATCCATTTGTGGTTTTTG
<i>MX1</i> -ShRNA-2R	AATTCAAAAACCACAAATGGAGTACAATAATCTCGA GATTATTGTAATCCATTTGTGG

Supplementary Table 4 SgRNA sequence used in this study

<i>APOE</i> -Sg-1F	CACCGTGCGTTGCTGGTCACATTCC
<i>APOE</i> -Sg-1R	AAACGGAATGTGACCAGCAACGCAC
<i>APOE</i> -Sg-2F	CACCGACAGTGTCTGCACCCAGCGC
<i>APOE</i> -Sg-2R	AAACGCGCTGGGTGCAGACACTGTC