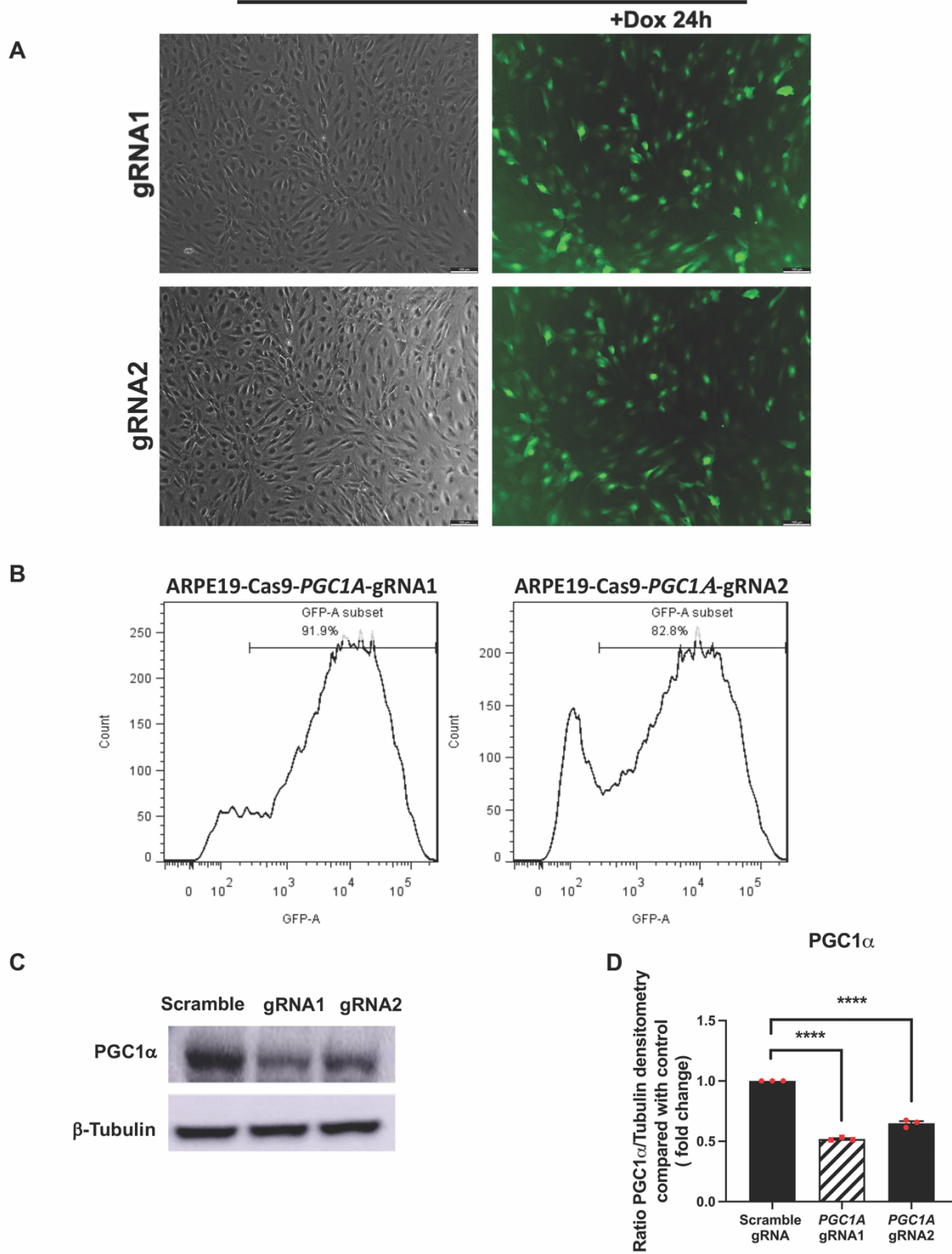


Supplementary Figure 1

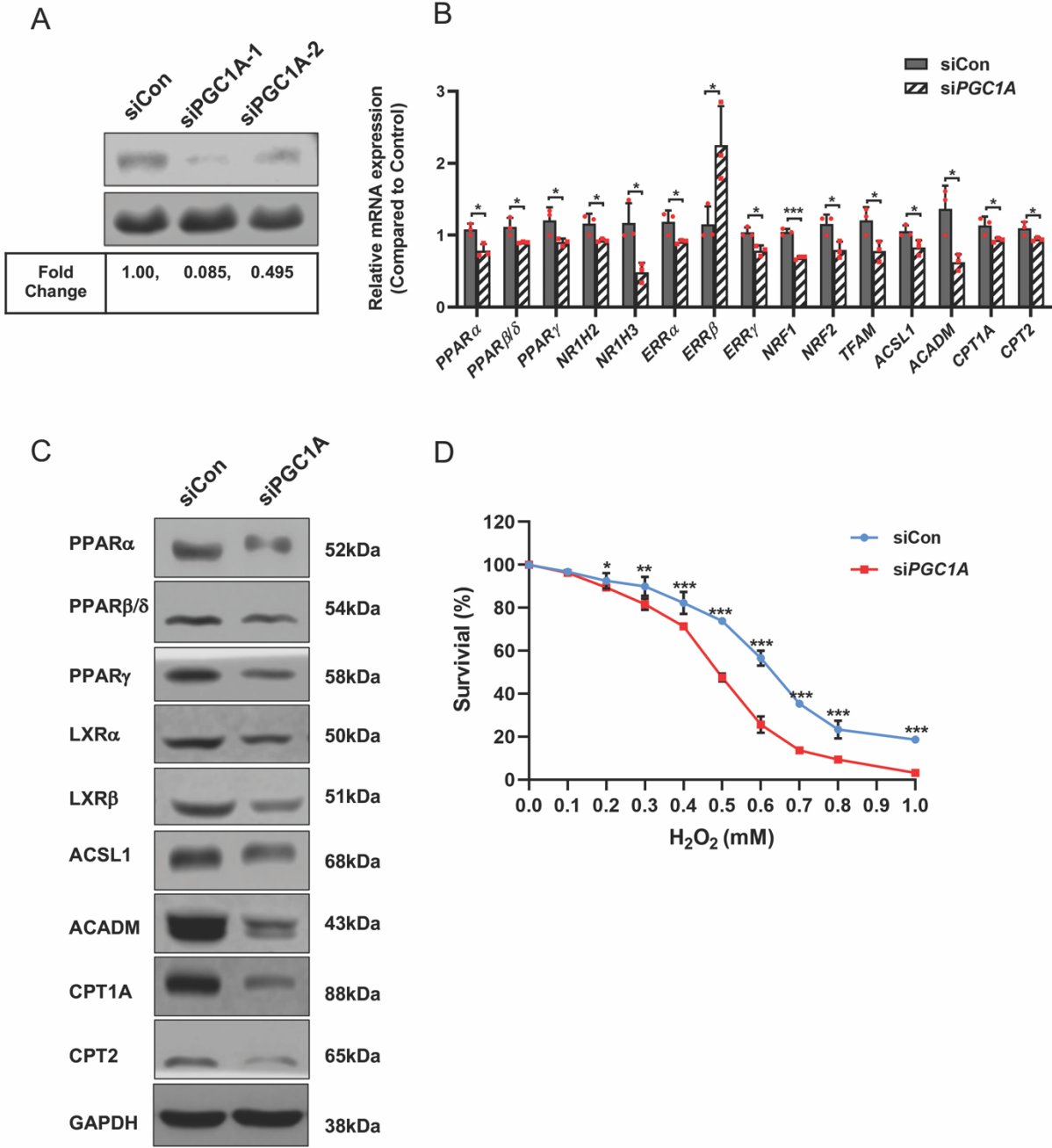
ARPE19-*PGC1A*-Cas9



S-Figure-1. Identification of ARPE19-*PGC1A* KO cells using CRISPR/Cas9 gene editing.

ARPE19 cells were transfected with CRISPR/Cas9-*PGC1A* sgRNAs vectors and selected by 2 μ g/ml puromycin for 2 weeks. **(A)** ARPE19-*PGC1A* KO cells were incubated with 2 μ M Doxycycline (DOX) for 24h to test the eGFP to confirm the expression of Cas9 (Scale bars:100 μ m). **(B)** Flow cytometry was performed to analyze the ratio of Cas9-eGFP cells upon 2 μ M doxycycline treatment for 48h. **(C-D)** *PGC1 α* protein levels in Scramble control and 2 different sgRNA groups were analyzed by Western Blots. *PGC1 α* protein was inhibited ~ 49% by sgRNA1 and 35% by sgRNA2 as compared with the control group. We chose gRNA1 for all of our experiments. The densitometry analysis was completed using ImageJ software. Ordinary one-way ANOVA with Dunnett's multiple comparisons were performed using GraphPad Prism 8.3.0. Graph represents mean \pm SD, n=3, **** P <0.0001.

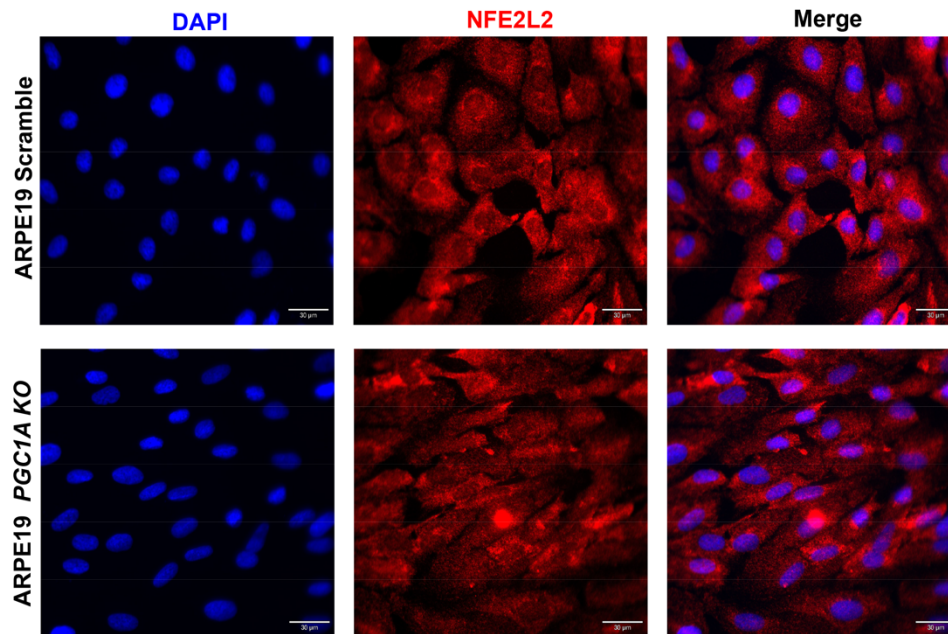
Supplementary Figure 2



S-Figure-2. Inhibition of *PGC1A* by siRNA reduced the expression of PPARs, LXRs and fatty acid β -oxidation related components, decreased the expression of mitochondrial biosynthesis related genes, and increased the susceptibility to oxidative stress.

ARPE19 cells were transfected with 2 different siRNAs, respectively, and the mRNA and protein were extracted in 72h to perform qPCR and Western blots. **(A)** *PGC1 α* protein was inhibited ~ 90% by siRNA1 and ~50% by siRNA2 as compared with the control group. We chose siRNA1 for the following experiments. **(B)** The mRNA levels of *PPAR α* , *PPAR β* , *PPAR γ* , *NR1H3* & *NR1H2*; *ERR α* , *ERR β* , *ERR γ* , *NRF1*, *NFE2L2*, *TFAM*; *ACSL1*, *ACADM*, *CPT1A* and *CPT2* (n=3) in ARPE19-si*PGC1A* and control cell lines. **(C)** The protein levels of the PPARs, LXRs, and fatty acid β -oxidation-related components. **(D)** Inhibition of *PGC1A* by siRNA1 declined ARPE19 cell viability with increasing concentration of H_2O_2 treatment for 24h, (n=3). An unpaired *t*-test was performed using GraphPad Prism 8.3.0. Graph represents mean \pm SEM, **P* \leq 0.05, ***P* \leq 0.01, *** *P* \leq 0.001.

S-Figure3



S-Figure-3. Inhibiting *PGC1A* does not affect the nuclear localization of NFE2L2 in ARPE19 cells.

Immunofluorescence images of NFE2L2 in ARPE19 PGC1A KO and the Scramble control cells.

Cells were seeded in a 35mm glass bottom confocal dish for 24h, and fixed in 4% formaldehyde for 15min at room temperature, then permeabilized with 0.25% Triton™ X-100 for 10 minutes. Cells were blocked with 5% BSA for 1hr at room temperature, followed by 3 washes with PBS, and overnight incubation with the primary antibody at 4°C. Cells were incubated with the secondary antibody the next day for 1hr at room temperature and mounted for imaging. The corresponding primary and secondary antibodies with their respective dilution factors are shown in Table. S2. NFE2L2 is stained in red (AlexaFluor 594), and nuclei were counterstained with DAPI (blue, 0100-20; Southern Biotech). Scale bars: 30 μm.

Table.S1. Primers used for qPCR analyses.

Primer Name	Primer Sequence (5'-3')
human <i>PPAR</i> α FOR	TTCGCAATCCATCGGCGAG
human <i>PPAR</i> α REV	CCACAGGATAAGTCACCGAGG
human <i>PPAR</i> β/δ FOR	CAGGGCTGACTGCAAACGA
human <i>PPAR</i> β/δ REV	CTGCCACAATGTCTCGATGTC
human <i>PPAR</i> γ FOR	TACTGTCCGTTTCAGAAATGCC
human <i>PPAR</i> γ REV	GTCAGCGGACTCTGGATTGAG
human <i>NR1H2</i> FOR	AGAACTAATGATCCAGCAGTTGG
human <i>NR1H2</i> REV	TTGCTTAGCGAAGTCCACGAT
human <i>NR1H3</i> FOR	CCTTCAGAACCCACAGAGATCC
human <i>NR1H3</i> REV	ACGCTGCATAGCTCGTTCC
human <i>CPT1A</i> FOR	ATCAATCGGACTCTGGAAACGG
human <i>CPT1A</i> REV	TCAGGGAGTAGCGCATGGT
human <i>CPT2</i> FOR	CATACAAGCTACATTTTCGGGACC
human <i>CPT2</i> REV	AGCCCGGAGTGTCTTCAGAA
human <i>ACSL1</i> FOR	CTTATGGGCTTCGGAGCTTTT
human <i>ACSL1</i> REV	CAAGTAGTGCGGATCTTCGTG
human <i>ACADM</i> FOR	ACAGGGGTTTCAGACTGCTATT
human <i>ACADM</i> REV	TCCTCCGTTGGTTATCCACAT
human <i>DGAT1</i> FOR	CAATCTGACCTACCGCGATCT
human <i>DGAT1</i> REV	TCGATGATGCGTGAGTAGTCC
human <i>DGAT2</i> FOR	GAATGGGAGTGGCAATGCTAT
human <i>DGAT2</i> REV	CCTCGAAGATCACCTGCTTGT
human <i>SOAT1</i> FOR	CAAGGCGCTCTCTTTAGATG
human <i>SOAT1</i> REV	GGTCCAACAACGGTAGGAAA

Primer Name	Primer Sequence (5'-3')
human <i>SOAT2</i> FOR	ATGGAAACACTGAGACGCACA
human <i>SOAT2</i> REV	GGTAGGATTGTATAGCCTCCCG
human <i>FATP2</i> FOR	GGCGCTCCTTATGGGTAACG
human <i>FATP2</i> REV	CTTGCCAGTATCTCTTCGACAG
human <i>FABP4</i> FOR	ACTGGGCCAGGAATTTGACG
human <i>FABP4</i> REV	CTCGTGGAAGTGACGCCTT
human <i>CD36</i> FOR	AAGCCAGGTATTGCAGTTCTTT
human <i>CD36</i> REV	GCATTTGCTGATGTCTAGCACA
human <i>ERRα</i> FOR	AGGGTTCCTCGGAGACAGAG
human <i>ERRα</i> REV	TCACAGGATGCCACACCATAG
human <i>ERRβ</i> FOR	TGGAGGCCGTCAGAAATACAA
human <i>ERRβ</i> REV	CAATGGCTTTTTAGCAGGTGGA
human <i>ERRγ</i> FOR	GCCCTCACTACACTGTGTGAC
human <i>ERRγ</i> REV	CCTGCTAATTTGGACTGGTCTT
human <i>NRF1</i> FOR	GCTGATGAAGACTCGCCTTCT
human <i>NRF1</i> REV	TACATGAGGCCGTTTCCGTTT
human <i>NFE2L2</i> FOR	TCCAGTCAGAAACCAGTGGAT
human <i>NFE2L2</i> REV	GAATGTCTGCGCCAAAAGCTG
human <i>TFAM</i> FOR	ATGGCGTTTCTCCGAAGCAT
human <i>TFAM</i> REV	TCCGCCCTATAAGCATCTTGA
human <i>ND1</i> FOR	CCTAGCCGTTTACTCAATCCT
human <i>ND1</i> REV	TGATGGCTAGGGTGACTTCAT
human <i>ACTB</i> FOR	CATCTCTTGCTCGAAGTCCA
human <i>ACTB</i> REV	ATCATGTTTGAGACCTTCAACA
human <i>GAPDH</i> FOR	GGAGCGAGATCCCTCCAAAAT
human <i>GAPDH</i> REV	GGCTGTTGTCATACTTCTCATGG

Primer Name	Primer Sequence (5'-3')
human <i>DRP1</i> FOR human <i>DRP1</i> REV	TTTGACACTTGTGGATTTGCCA AGTGACAGCGAGGATAATGGA
human <i>OPA1</i> FOR human <i>OPA1</i> REV	TGTGAGGTCTGCCAGTCTTTA TGCCTTAATTGGGGTTCGTTG
human <i>NDUFS2</i> FOR human <i>NDUFS2</i> REV	GCTGTTATGTACCCAAGCAAAGA TCCCCACTCAATTCCATCACT
human <i>NDUFS8</i> FOR human <i>NDUFS8</i> REV	CCATCAACTACCCGTTTCGAGA CCGCAGTAGATGCACTTGG
human <i>CDS1</i> FOR human <i>CDS1</i> REV	AGTTCCTCATTCGCTACCATAGA GGTGTGACTGAGTGACAGTTATC
human <i>PGS1</i> FOR human <i>PGS1</i> REV	TCGTGATGGCATCCCTCTAC CCCCGCGTGAAGTCTAAGA
human <i>PTPMT1</i> FOR human <i>PTPMT1</i> REV	CAGAGGAGGCTGTAAGAGCCA TGTGGATGTATGACCGGATCT
human <i>CRLS1</i> FOR human <i>CRLS1</i> REV	AGCAGTCCAGTTAATCTTGGTG AGTCTTCCGGCCATAATGATAGT
human <i>TAFFAZIN</i> FOR human <i>TAFFAZIN</i> REV	CACCGTGTCCAATCACCAGTC TCCAACGCATCAACTTCAGGT
human <i>SOD1</i> FOR human <i>SOD1</i> REV	AGGGCATCATCAATTTTCGAGC GCCACCGTGTTTTCTGGA
human <i>SOD2</i> FOR human <i>SOD2</i> REV	CAGACCTGCCTTACGACTATGG CGTTCAGGTTGTTACGTAGG
human <i>CAT</i> FOR human <i>CAT</i> REV	ACTTTGAGGTCACACATGACATT CTGAACCCGATTCTCCAGCA

Table. S2. Antibodies used for Western blots and Immunofluorescence.

Antibody	Source	Vendor	Cat. No	dilution
PGC1 α	Rabbit	Millipore Sigma, USA	AB3242	1:1000
ACADM	Rabbit	Proteintech Group, USA	55210-1-AP	1:1000
CPT1A	Rabbit	Proteintech Group, USA	15184-1-AP	1:1000
ACSL1	Rabbit	Proteintech Group, USA	13989-1-AP	1:1000
PPAR α	Rabbit	Proteintech Group, USA	15540-1-AP	1:600
PPAR β/δ	Mouse	Proteintech Group, USA	60193-1-Ig	1:1000
NR1H3	Rabbit	Proteintech Group, USA	14351-1-AP	1:2000
NR1H2	Mouse	Proteintech Group, USA	60345-1-Ig	1:800
FABP4	Rabbit	Proteintech Group, USA	12802-1-AP	1:5000
SOAT2	Rabbit	Proteintech Group, USA	21852-1-AP	1:1000
SOAT1	Rabbit	Cell signal technology, USA	35695	1:1000
CPT2	Rabbit	Proteintech Group, USA	26555-1-AP	1:1000
DGAT1	Rabbit	Proteintech Group, USA	11561-1-AP	1:1000
DGAT2	Rabbit	Proteintech Group, USA	17100-1-AP	1:1000
PTPMT1	Rabbit	Proteintech Group, USA	11493-1-AP	1:300
FATP2	Rabbit	Proteintech Group, USA	14048-1-AP	1:2000
CD36	Rabbit	Proteintech Group, USA	18836-1-AP	1:1000
PPAR γ	Rabbit	Proteintech Group, USA	16643-1-AP	1:2000
PGS1	Rabbit	Proteintech Group, USA	17149-1-AP	1:500
CRLS1	Rabbit	Proteintech Group, USA	51055-1-AP	1:300
TAFFAZIN	Mouse	Santa Cruz Biotechnology, USA	SC-365810	1:500
GAPDH	Rabbit	Cell Signaling Technology, USA	5174S	1:8000
anti-Mouse IgG	Goat	Jackson ImmunoResearch	115-035-003	1:4000
anti-Rabbit IgG	Goat	Jackson ImmunoResearch	111-035-003	1:4000

Antibody	Source	Vendor	Cat. No	dilution
ABCA1	Rabbit	Cell signaling Technology, USA	96292S	1:1000
HMGCR	Rabbit	Thermo Fisher Scientific, USA	PA5-37367	1:1000
ABCG1	Rabbit	Proteintech Group, USA	13578-1-AP	1:1000
ABCG5	Rabbit	Proteintech Group, USA	27722-1-AP	1:800
LDLR	Rabbit	Proteintech Group, USA	10785-1-AP	1:2000
Phospho-HMGCR (Ser872)	Rabbit	Thermo Fisher Scientific, USA	BS-4063R	1:1000
SOD2	Rabbit	Cell signaling Technology, USA	13141S	1:1000
Catalase	Rabbit	Cell signaling Technology, USA	14097S	1:1000
AMPK α	Rabbit	Cell signaling Technology, USA	5832S	1:1000
Phospho-AMPK α (Thr172)	Rabbit	Cell signaling Technology, USA	2535S	1:1000
NFE2L2	Rabbit	Proteintech Group, USA	80593-1-RR	WB 1:1000 IF 1:500
Donkey anti-Rabbit IgG Antibody, Alexa Fluor® 594	Donkey	Thermo Fisher Scientific, USA	R37119	1:2000