

Supplementary Information

PDK4 drives abdominal aortic aneurysm by promoting smooth muscle cell metabolic reprogramming and NLRP3-mediated pyroptosis

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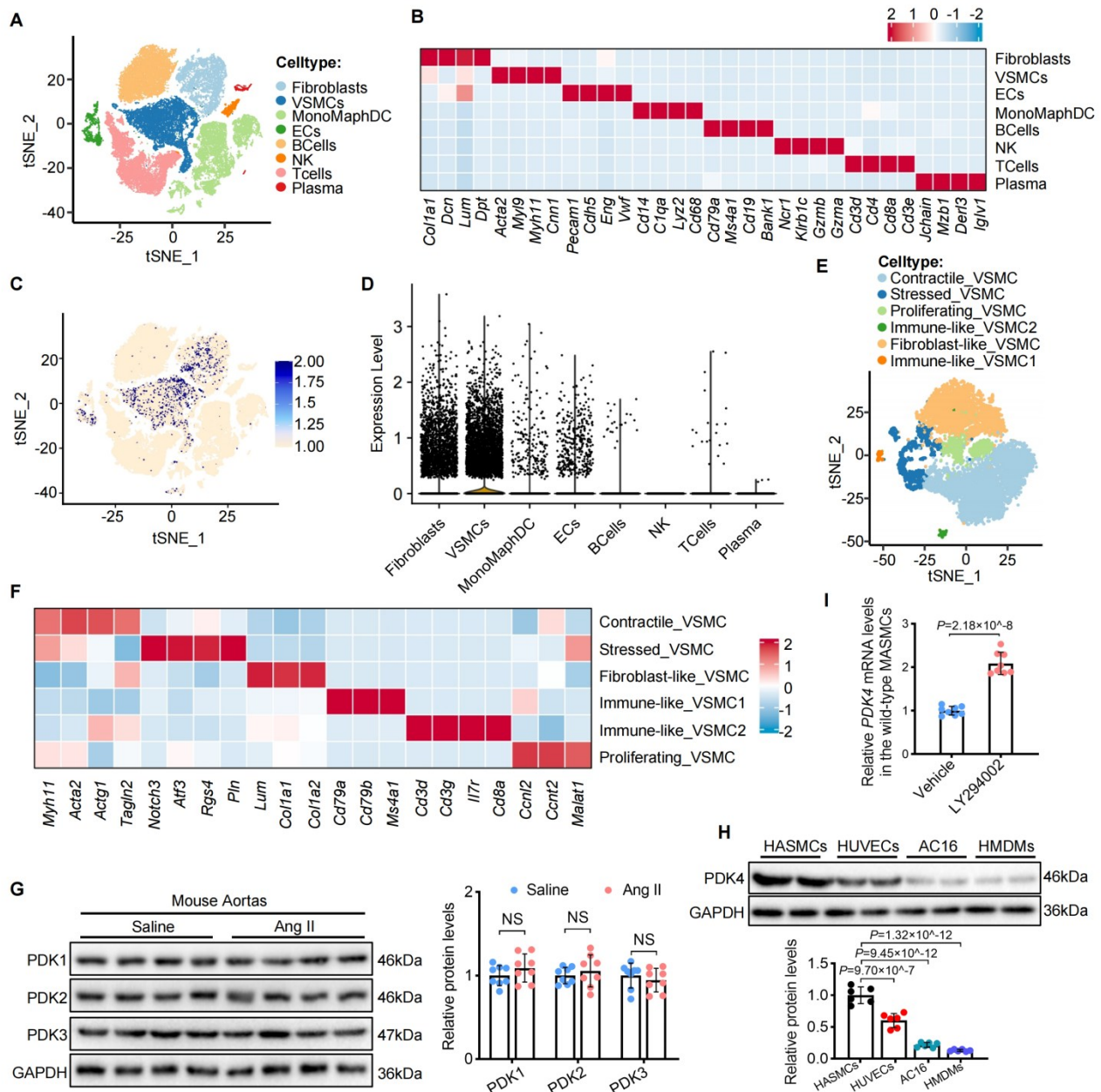


Fig. S1 | PDK4 is the predominant dysregulated isoform in AAA tissue. **A** t-distributed stochastic neighbor embedding (*t*-SNE) plot displaying all cells from mouse aortas, colored according to the eight identified cell types (Gene Expression Omnibus accession no. GSE239620). **B** Mean expression of marker genes across major cell types. **C** t-SNE plots showing single-cell gene expression of *PDK4* across cell clusters from the GEO data. **D** Violin plot of *PDK4* expression levels across different cell groups. **E** t-SNE visualization of VSMC subclusters with color-coded classification. **F** Mean expression of marker genes across six VSMC subclusters. **G** Relative PDK1, PDK2, and PDK3 protein

levels were measured by Western blot analysis in the abdominal aortas of mice treated with AAV-*PCSK9^{DY}*/Ang II for 28 days or AAV-*PCSK9^{DY}*/saline for 28 days (n=8 biological replicates). **H** Relative PDK4 protein levels in different cells, including HASMCs, HUVECs, AC16, and HMDMs (n=6 biological replicates). **I** Relative *PDK4* mRNA levels in MASMCS isolated from wild-type mice treated with vehicle or LY294002 (50 μ M, 48 h) (n=8 biological replicates). Data are presented as mean $\pm$ SD. (G, I) Two-sided Unpaired Student's *t*-test; (H) one-way ANOVA followed by Tukey's multiple-comparisons test. Source data are provided as a Source Data file.

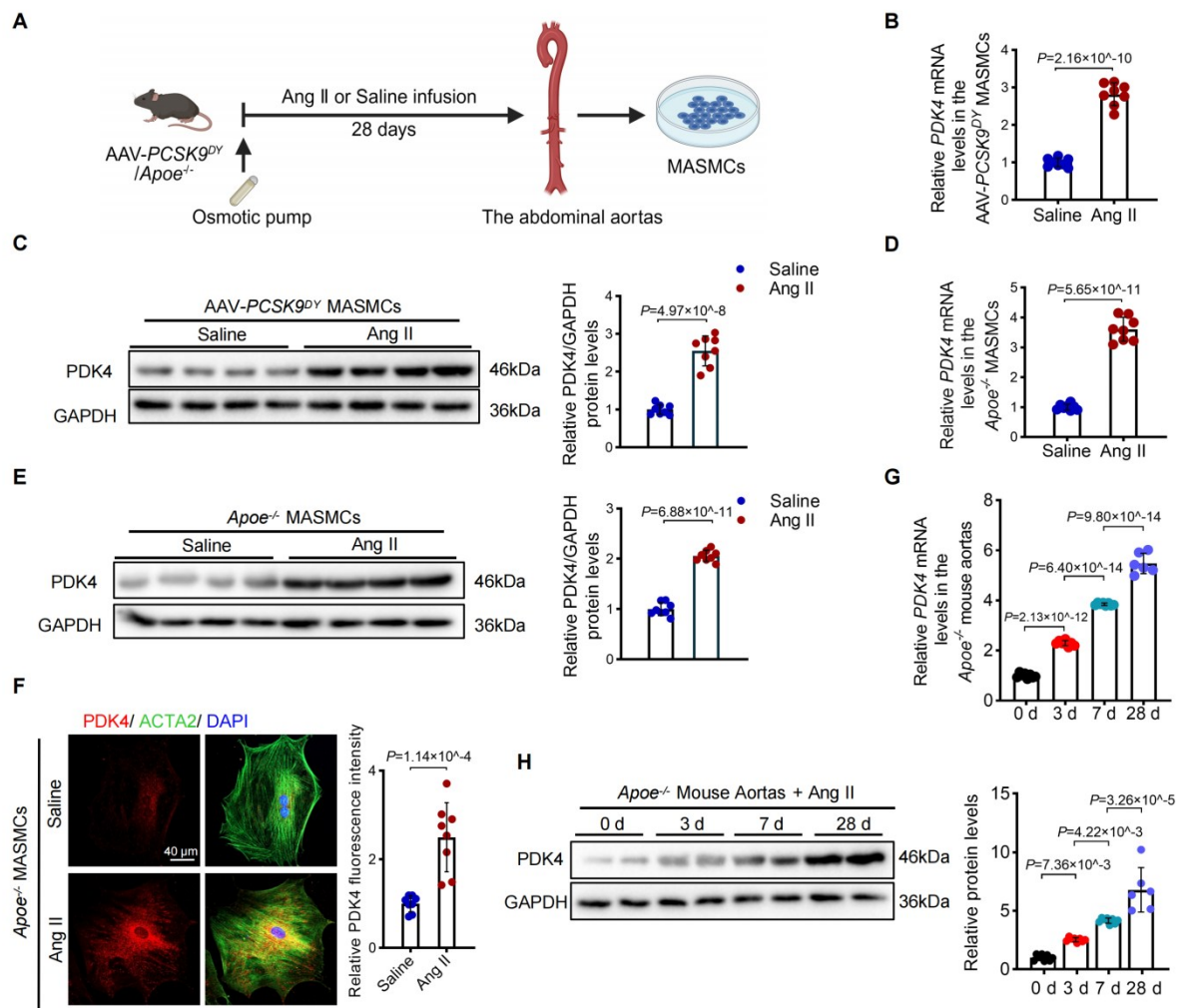


Fig. S2 | PDK4 is upregulated in MAMCs with Ang II. A Schematic diagram of the extraction method and treatment for MAMCs from AAV-PCSK9^{DY} or Apoe^{-/-} mice. Created with BioRender. Liu, X. (2026) <https://BioRender.com/po5y0ge>. B-C Relative PDK4 mRNA and protein levels in MAMCs isolated from AAV-PCSK9^{DY} mice treated with Ang II or saline for 28 days (n=8 biological replicates). D-E Relative PDK4 mRNA and protein levels in MAMCs isolated from Apoe^{-/-} mice treated with Ang II or saline for 28 days (n=8 biological replicates). F PDK4 and ACTA2 immunofluorescence in MAMCs isolated from Apoe^{-/-} mice treated with Ang II or saline for 28 days (n=8 biological replicates). G-H Relative PDK4 mRNA and protein levels were measured by RT-qPCR and Western blot analysis in the abdominal aortas of Apoe^{-/-} mice at different time points (0, 3,

7 and 28 days) after Ang II treatment (n=8 biological replicates for 0, 3, 7 days; n=6 biological replicates for 28 days). Data are presented as mean $\pm$ SD. (B-F) Two-sided Unpaired Student's *t*-test; (G, H) one-way ANOVA followed by Tukey's multiple-comparisons test. Source data are provided as a Source Data file.

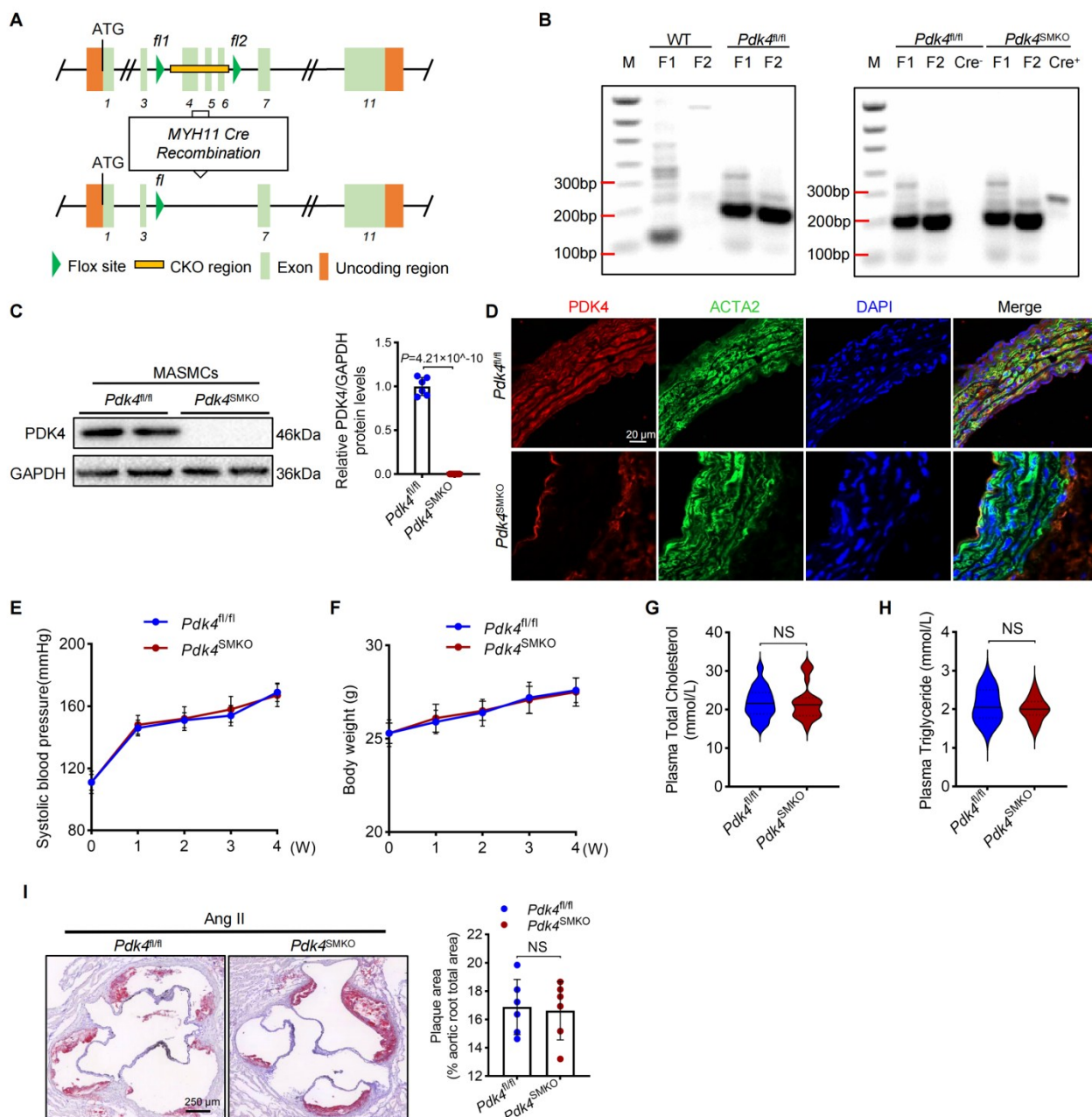


Fig. S3 | Construction and validation of the VSMC-specific PDK4 knockout mouse model. **A** Strategy for generation of *Pdk4*^{SMKO} mice. **B** Mice were PCR-genotyped using specific primers for fl1 (F1), fl2 (F2), or *Myh11*-Cre. Mice harboring fl1, fl2, and *Myh11*-Cre were considered *Pdk4*^{SMKO}; those harboring fl1 and fl2, but not *Myh11*-Cre, were considered *Pdk4*^{fl/fl}. **C** Western blot analysis showing the PDK4 protein levels in VSMCs isolated from *Pdk4*^{fl/fl} and *Pdk4*^{SMKO} mice (n=6 biological replicates). **D** Representative images of PDK4 and ACTA2 expression using immunofluorescence

staining in suprarenal abdominal aortas from mice of *Pdk4*^{fl/fl} and *Pdk4*^{SMKO} (n=6 biological replicates).

E-H Systolic blood pressure, body weight, and serum TC and TG levels in *Pdk4*^{fl/fl} and *Pdk4*^{SMKO} mice treated with AAV-*PCSK9*^{DY}/Ang II (n=18 for *Pdk4*^{fl/fl} and n=22 for *Pdk4*^{SMKO}, mice that died of aortic rupture were not included in the measurements). **I** Representative Oil Red O-stained aortic root sections and quantification in *Pdk4*^{fl/fl} and *Pdk4*^{SMKO} mice (n=6 biological replicates). Data are presented as mean ± SD. (G) Two-sided Mann–Whitney *U* test (exact method); (C, E-F, H-I) Two-sided Unpaired Student's *t*-test. NS, nonsignificant. Source data are provided as a Source Data file.

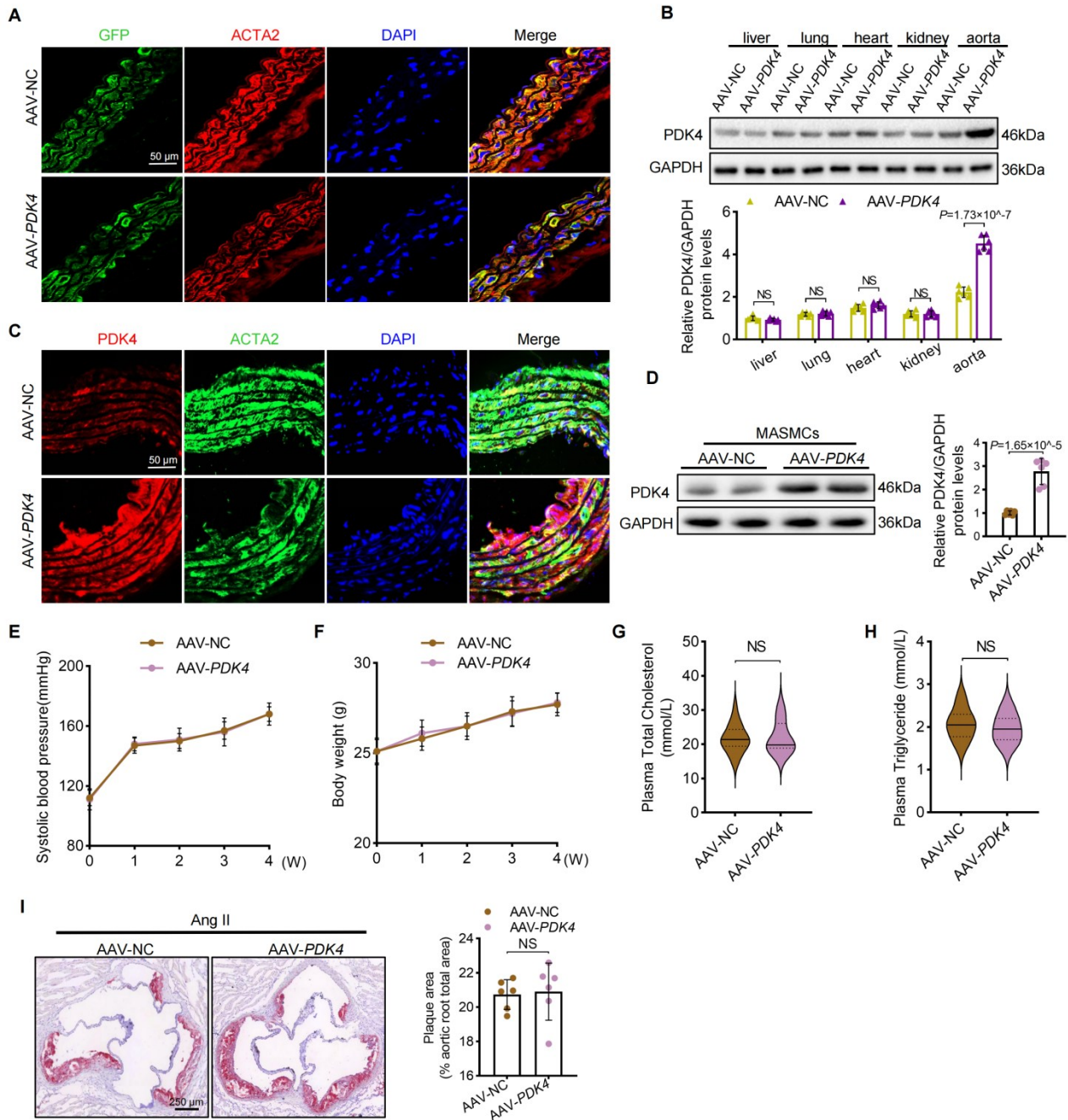


Fig. S4 | Validation of the VSMC-specific PDK4 overexpression mouse model. **A** Representative immunofluorescence images showing green fluorescent protein (GFP) and ACTA2 expression in suprenal abdominal aortas from mice injected with AAV-NC or AAV-PDK4 (n=6 biological replicates). **B** PDK4 protein levels in the liver, lung, heart, kidney, and aorta of AAV-NC and AAV-PDK4 mice (n=6 biological replicates). **C** Representative immunofluorescence staining of PDK4 and ACTA in suprenal abdominal aortas from mice injected with AAV-NC and AAV-PDK4 (n=6 biological replicates). **D** PDK4 protein levels in MASCs of AAV-NC and AAV-PDK4 mice (n=6 biological replicates). **E** Systolic blood pressure (mmHg) over 4 weeks (W) for AAV-NC and AAV-PDK4 mice (n=6 biological replicates). **F** Body weight (g) over 4 weeks (W) for AAV-NC and AAV-PDK4 mice (n=6 biological replicates). **G** Plasma total cholesterol (mmol/L) for AAV-NC and AAV-PDK4 mice (n=6 biological replicates). **H** Plasma triglyceride (mmol/L) for AAV-NC and AAV-PDK4 mice (n=6 biological replicates). **I** Plaque area (% aortic root total area) for AAV-NC and AAV-PDK4 mice (n=6 biological replicates) after Ang II treatment.

biological replicates). **D** PDK4 protein levels in VSMCs isolated from AAV-NC and AAV-*PDK4* mice (n=6 biological replicates). **E-H** Systolic blood pressure, body weight, and serum TC and TG levels in AAV-NC and AAV-*PDK4* mice (n=18 for AAV-NC and n=12 for AAV-*PDK4*, mice that died from aortic rupture were excluded from these measurements). **I** Representative Oil Red O-stained aortic root sections and quantification in AAV-NC and AAV-*PDK4* mice (n=6 biological replicates). Data are presented as mean $\pm$ SD. (B, D-F, H-I) Two-sided Unpaired Student's *t*-test; (G) Two-sided Mann–Whitney *U* test (exact method). NS, nonsignificant. Source data are provided as a Source Data file.

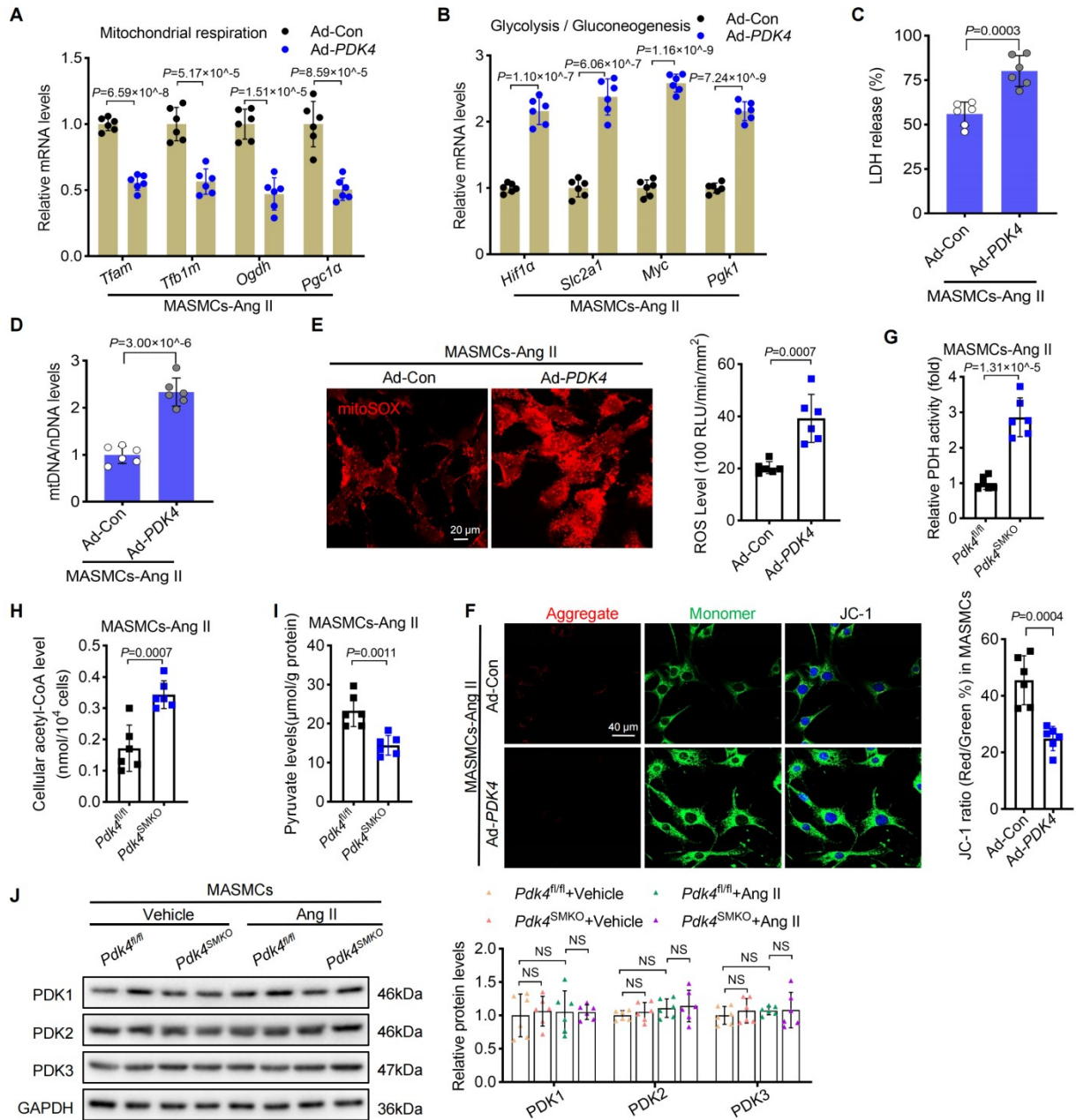


Fig. S5 | PDK4 overexpression alters mitochondrial respiration and ROS production. A-F MASCs transfected with Ad-NC or Ad-PDK4, followed by treatment with Ang II (1 μ M, 48 h). **A** Relative mRNA levels of genes related to mitochondrial respiration were measured by RT-qPCR analysis in the MASCs (n=6 biological replicates). **B** Relative mRNA levels of genes related to glycolysis/gluconeogenesis were measured by RT-qPCR analysis in the MASCs (n=6 biological replicates). **C** LDH levels in the MASCs (n=6 biological replicates). **D** mtDNA/nDNA levels in the MASCs (n=6 biological replicates). **E** Representative mitochondria-derived ROS fluorescence

probe (MitoSOX) staining in MASMCs (n=6 biological replicates). **F** Representative JC-1 staining and quantification in MASMCs (n=6 biological replicates). **G-I** Levels of PDH activity, acetyl-CoA and pyruvate in MASMCs isolated from *Pdk4^{fl/fl}* and *Pdk4^{SMKO}* mice, followed by treatment with Ang II (1 μ M, 48 h) (n=6 biological replicates). **J** Relative PDK1, PDK2, and PDK3 protein levels were measured by Western blot analysis in MASMCs isolated from *Pdk4^{fl/fl}* and *Pdk4^{SMKO}* mice, followed by treatment with vehicle or Ang II (1 μ M, 48 h) (n=6 biological replicates). Data are presented as mean $\pm$ SD. (A-I) Two-sided Unpaired Student's *t*-test. (J) two-way ANOVA followed by Tukey's multiple-comparisons test. NS, nonsignificant. Source data are provided as a Source Data file.

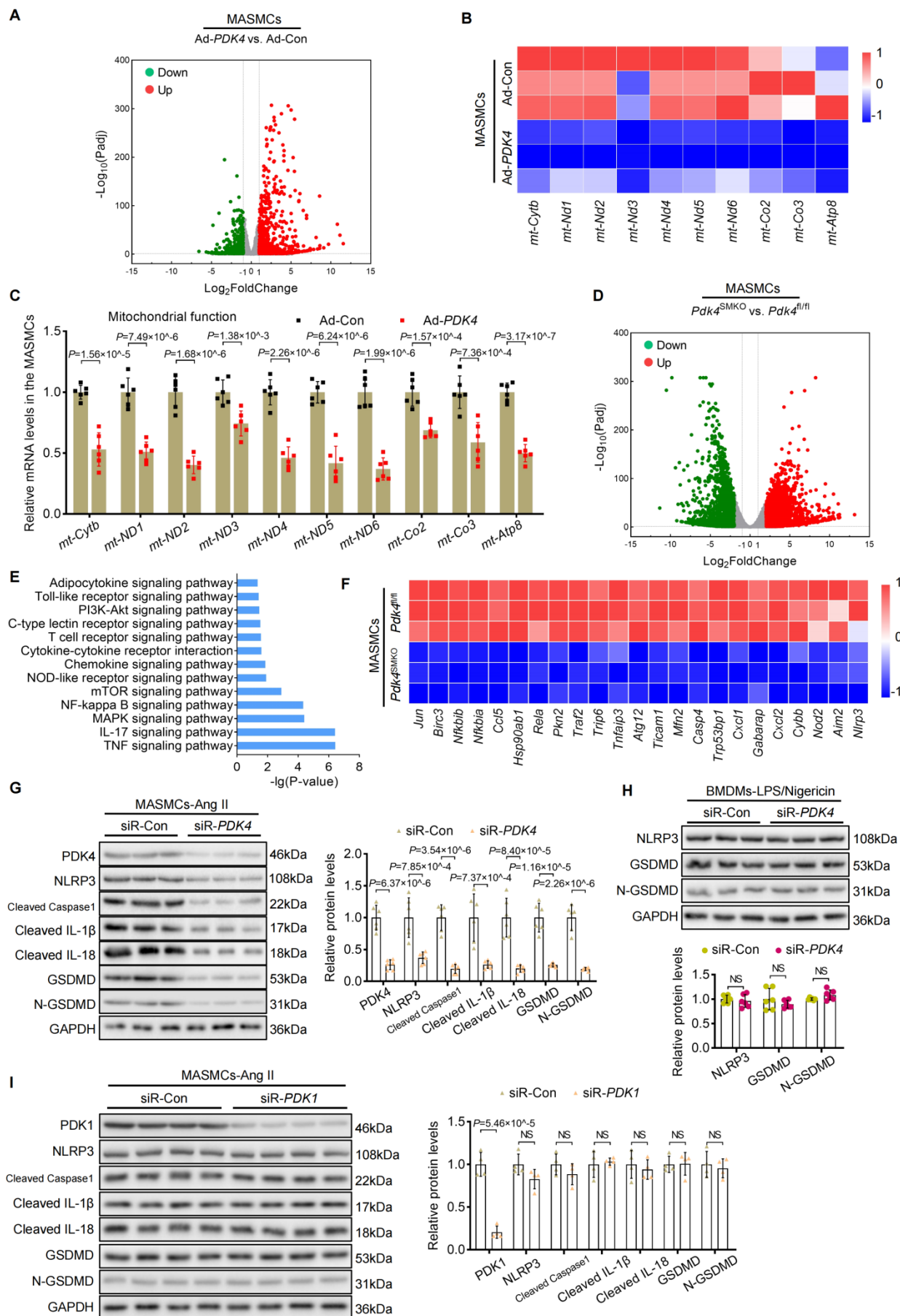


Fig. S6 | Transcriptomic profiling and validation of PDK4-regulated pathways in MASMCs. A Volcano plots of the differentially expressed genes in MASMCs transfected with Ad-Con or Ad-*PDK4*, followed by treatment with Ang II (1 μ M, 48 h) (n=3 biological replicates). **B** Heatmap comparing the gene expression profiles of MASMCs transfected with Ad-Con or Ad-*PDK4*, followed by treatment with Ang II (1 μ M, 48 h) (blue indicates downregulation; red indicates upregulation). **C** Relative mRNA levels of mtDNA genes were measured by RT-qPCR analysis in MASMCs transfected with Ad-Con or Ad-*PDK4*, followed by treatment with Ang II (1 μ M, 48 h) (n=6 biological replicates). **D** Volcano plots of the differentially expressed genes in MASMCs isolated from *Pdk4*^{SMKO} and *Pdk4*^{fl/fl} mice and treated with Ang II (1 μ M, 48 h) (n=3 biological replicates). **E** KEGG analysis of downregulated pathways identified by RNA-seq in MASMCs isolated from *Pdk4*^{SMKO} and *Pdk4*^{fl/fl} mice after Ang II treatment (1 μ M, 48 h) (n=3 biological replicates). **F** Heat map of RNA-seq data from MASMCs isolated from *Pdk4*^{SMKO} and *Pdk4*^{fl/fl} mice and treated with Ang II (1 μ M, 48 h) (n=3 biological replicates) (blue indicates downregulation; red indicates upregulation). **G** Representative Western blot and quantification of PDK4, NLRP3, Cleaved Caspase1, Cleaved IL-1 β , Cleaved IL-18, GSDMD and N-GSDMD protein levels in MASMCs transfected with siR-Con or siR-*PDK4*, followed by treatment with Ang II (1 μ M, 48 h) (n=6 biological replicates). **H** Representative Western blot and quantification of NLRP3, GSDMD and N-GSDMD protein levels in BMDMs transfected with siR-Con or siR-*PDK4*, followed by treatment with LPS (100 ng/mL, 4 h) and nigericin (10 μ M, 30 min) (n=6 biological replicates). **I** Representative Western blot and quantification of PDK1, NLRP3, Cleaved Caspase-1, Cleaved IL-1 β , Cleaved IL-18, GSDMD, and N-GSDMD protein levels in MASMCs transfected with siR-Con or siR-*PDK1*, followed by Ang II treatment (1 μ M, 48 h) (n=6 biological replicates). Data are presented as mean $\pm$ SD. (C, G, H) Two-sided Unpaired Student's *t*-

test. (I) Two-sided Unpaired Student's t -test or Mann–Whitney U test (exact method). NS, nonsignificant. Source data are provided as a Source Data file.

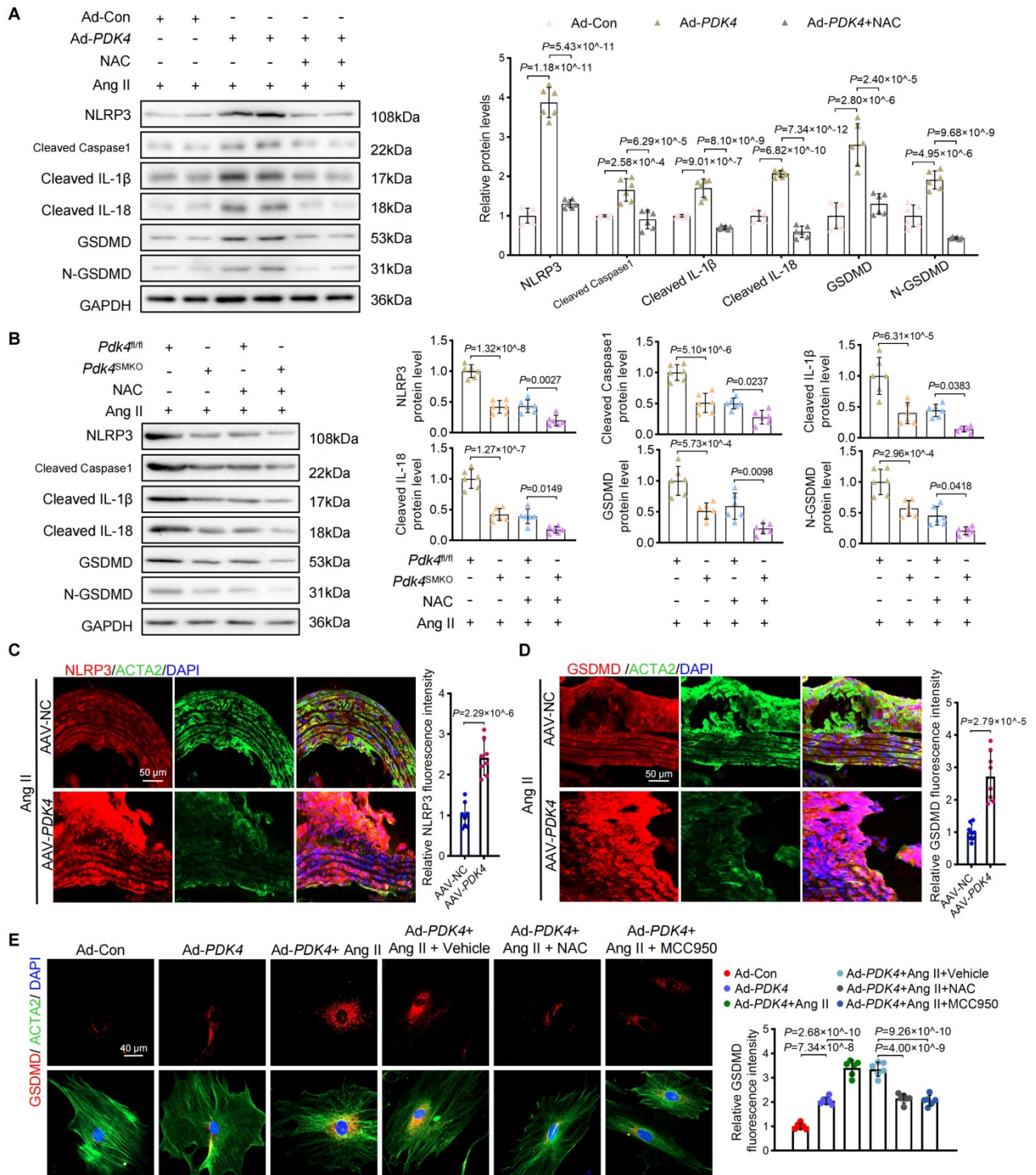


Fig. S7 | *PDK4* overexpression promotes pyroptosis in VSMCs. A MASCs were serum-starved and simultaneously transfected with Ad-*PDK4* or Ad-Con for 48 h, followed by treatment with NAC (10 mM, 1 h) and then Ang II (1 μ M, 48 h). Representative Western blot and quantification of NLRP3, Cleaved Caspase1, Cleaved IL-1 β , Cleaved IL-18, GSDMD, and N-GSDMD protein levels (n=6

biological replicates). **B** Representative Western blot and quantification of NLRP3, Cleaved Caspase1, Cleaved IL-1 β , Cleaved IL-18, GSDMD and N-GSDMD in MASMCs isolated from *Pdk4*^{SMKO} and *Pdk4*^{fl/fl} mice and treated with NAC (10 mM, 1 h) followed by Ang II (1 μ M, 48 h) (n=6 biological replicates). **C-D** Immunofluorescence staining of GSDMD, NLRP3, and ACTA2 was performed in suprarenal abdominal aortas from AAV-NC and AAV-*PDK4* mice treated with AAV-*PCSK9*^{DY}/Ang II for 28 days (n=8 biological replicates, representative images from eight biologically independent samples are shown). **E** Immunofluorescence staining for GSDMD and ACTA2 was performed in MASMCs transfected with Ad-Con or Ad-*PDK4* for 48 h, pre-treated with either NAC (10 mM) or MCC950 (10 μ M) for 1 h, and subsequently stimulated with Ang II (1 μ M) for 48 h (n=6 biological replicates). Data are presented as mean $\pm$ SD. (A-B, E) one-way ANOVA followed by Tukey's multiple-comparisons test. (C-D) Two-sided Unpaired Student's *t*-test. NS, nonsignificant. Source data are provided as a Source Data file.

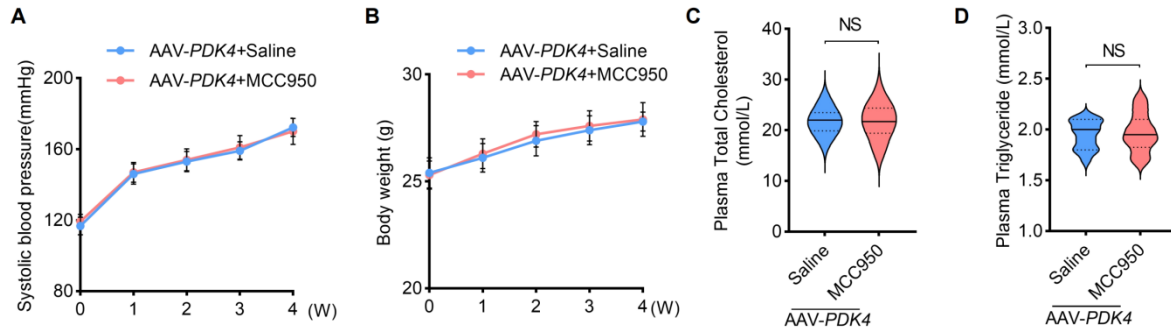


Fig. S8 | MCC950 has limited effects on body weight, systolic blood pressure, and serum lipids.

A-D Eight-week-old male C57BL/6J mice were injected with AAV-*PCSK9*^{DY} and fed a Western diet. Two weeks later, mice were treated with AAV-*PDK4* and MCC950 or saline. Two weeks later, mice were infused with Ang II (1,500 ng/kg/min) for an additional 4 weeks. **A-D** Systolic blood pressure, body weight, serum TC, and serum TG levels in mice injected with or treated with AAV-*PDK4* + saline or AAV-*PDK4* + MCC950 (n=13 for AAV-*PDK4* + saline and n=20 for AAV-*PDK4* + MCC950, mice that died from aortic rupture were excluded from these measurements). Data are presented as mean $\pm$ SD. (A-D) Two-sided Unpaired Student's *t*-test. NS, nonsignificant. Source data are provided as a Source Data file.

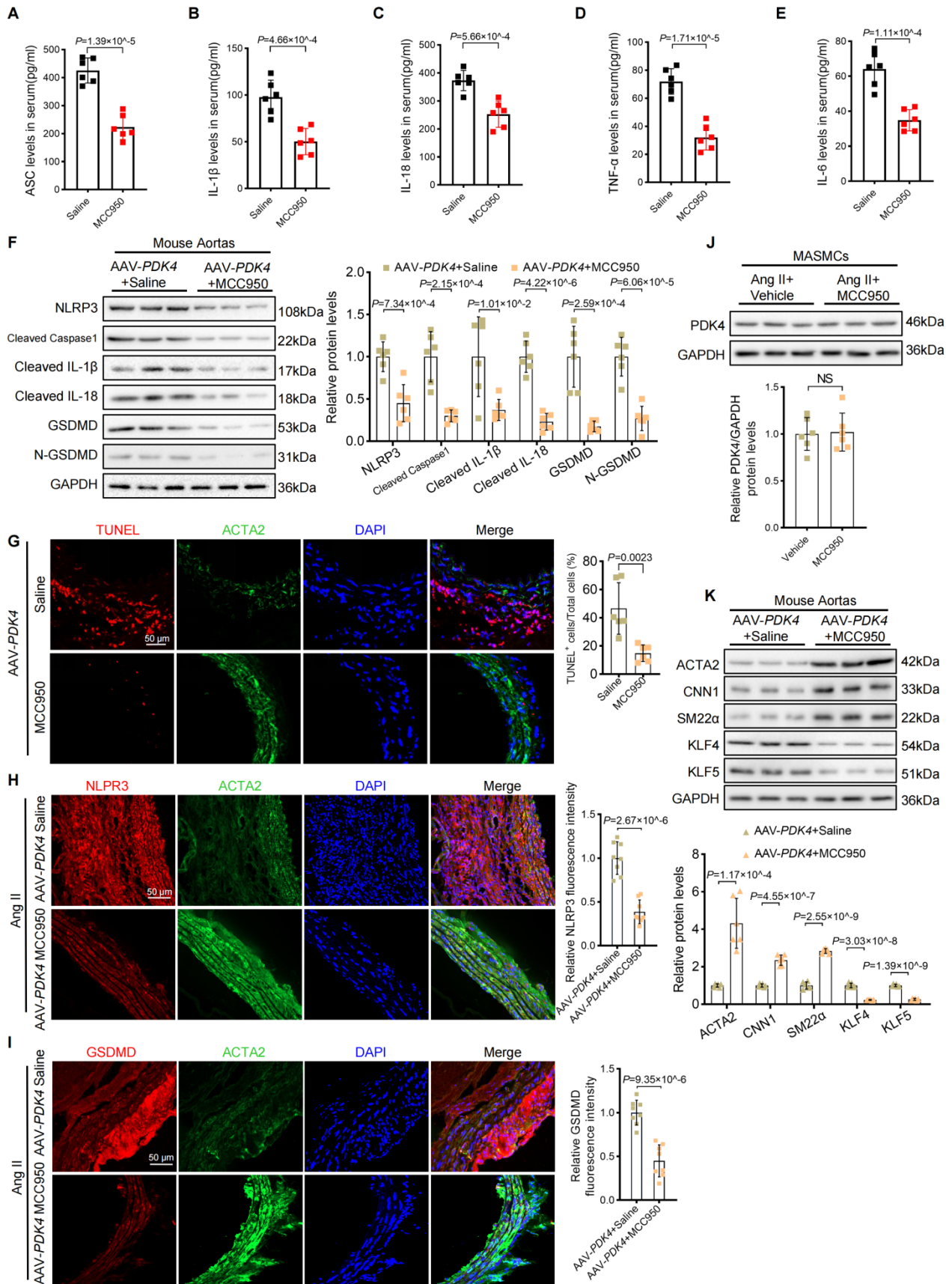


Fig. S9 | MCC950 alleviates AAA formation by attenuating PDK4-induced NLRP3 inflammasome activation and pyroptotic cell death. **A-I** Eight-week-old male C57BL/6J mice were injected with AAV-*PCSK9^{DY}* and fed a Western diet. Two weeks later, mice were treated with AAV-PDK4 and MCC950 or saline. After an additional 2 weeks, mice were infused with Ang II (1,500 ng/kg/min) for 4 weeks (n = 22 for MCC950 and n = 22 for saline). **A-E** Enzyme-linked immunosorbent assay (ELISA) was utilized to measure the serum levels of ASC, IL-1 β , IL-18, TNF- α and IL-6 in AAV-*PDK4* + saline and AAV-*PDK4* + MCC950 mice treated with AAV-*PCSK9^{DY}*/Ang II (n=6 biological replicates). **F** Representative Western blot and quantification of NLRP3, Cleaved Caspase1, Cleaved IL-1 β , Cleaved IL-18, GSDMD and N-GSDMD protein levels in the abdominal aortas from AAV-*PDK4* + saline and AAV-*PDK4* + MCC950 mice treated with AAV-*PCSK9^{DY}*/Ang II (n=6 biological replicates). **G** Representative images of TUNEL staining in suprarenal abdominal aortas from AAV-*PDK4* + saline and AAV-*PDK4* + MCC950 mice treated with AAV-*PCSK9^{DY}*/Ang II (n=6 biological replicates). **H-I** Immunofluorescence staining of GSDMD, NLRP3, and ACTA2 in suprarenal abdominal aortas from AAV-*PDK4* + saline and AAV-*PDK4* + MCC950 mice treated with AAV-*PCSK9^{DY}*/Ang II (n=8 biological replicates). **J** Representative Western blot and quantification of PDK4 protein levels in MASMCs pre-treated with MCC950 (10 μ M) for 1 h, followed by stimulation with Ang II (1 μ M) for 48 h (n=6 biological replicates). **K** Representative Western blot and quantification of ACTA2, CNN1, SM22 α , KLF4, and KLF5 protein levels in abdominal aortas from AAV-*PDK4* + saline- and AAV-*PDK4* + MCC950-treated mice after AAV-*PCSK9^{DY}*/Ang II treatment (n=6 biological replicates). Data are presented as mean $\pm$ SD. (A-K) Two-sided Unpaired Student's *t*-test. NS, nonsignificant. Source data are provided as a Source Data file.

Supplementary Tables

Supplementary Table 1. SNP genotyping analysis used in this study.

dbSNP ID	C57BL/6J Alleles	<i>Pdk4</i> ^{SMKO} (n=5 biological replicates)	<i>Pdk4</i> ^{fl/fl} (n=5 biological replicates)	Genetic Background
rs13475886	T/T	T/T	T/T	C57BL/6J
rs13476337	A/A	A/A	A/A	C57BL/6J
rs13476359	G/G	G/G	G/G	C57BL/6J
rs33142586	A/A	A/A	A/A	C57BL/6J
rs13476956	C/C	C/C	C/C	C57BL/6J
rs13477019	T/T	T/T	T/T	C57BL/6J
rs13477132	G/G	G/G	G/G	C57BL/6J
rs13477622	T/T	T/T	T/T	C57BL/6J
rs13477746	T/T	T/T	T/T	C57BL/6J
rs13478320	C/C	C/C	C/C	C57BL/6J
rs3662161	A/A	A/A	A/A	C57BL/6J
rs33208334	T/T	T/T	T/T	C57BL/6J
rs30764547	T/T	T/T	T/T	C57BL/6J
rs13478783	A/A	A/A	A/A	C57BL/6J
rs6157367	T/T	T/T	T/T	C57BL/6J
rs13479522	A/A	A/A	A/A	C57BL/6J
rs13479540	A/A	A/A	A/A	C57BL/6J
rs3709624	T/T	T/T	T/T	C57BL/6J
rs13480100	T/T	T/T	T/T	C57BL/6J
rs13480109	A/A	A/A	A/A	C57BL/6J
rs13480122	T/T	T/T	T/T	C57BL/6J
rs13480575	T/T	T/T	T/T	C57BL/6J
rs13480619	T/T	T/T	T/T	C57BL/6J
rs29359333	G/G	G/G	G/G	C57BL/6J
rs13480628	T/T	T/T	T/T	C57BL/6J
rs13459122	T/T	T/T	T/T	C57BL/6J
rs13480759	C/C	C/C	C/C	C57BL/6J
rs3659787	G/G	G/G	G/G	C57BL/6J
rs13481014	T/T	T/T	T/T	C57BL/6J
rs13481117	G/G	G/G	G/G	C57BL/6J
rs13481403	G/G	G/G	G/G	C57BL/6J
rs13481439	A/A	A/A	A/A	C57BL/6J
rs223935946	T/T	T/T	T/T	C57BL/6J
rs13481569	G/G	G/G	G/G	C57BL/6J
rs13481634	A/A	A/A	A/A	C57BL/6J
rs13481676	A/A	A/A	A/A	C57BL/6J

dbSNP, Database of Single Nucleotide Polymorphisms.

Supplementary Table 2. Characteristics of patients included in this study.

Characteristics	AAA (n = 8)
Age (years)	63.5 ± 4.504
Male (n, %)	7 (87.5)
Body mass index (kg/m ²)	25.03 ± 1.061
History of smoking (n, %)	3 (37.5)
Hypertension (n, %)	6 (75.0)
Diabetes mellitus (n, %)	1 (12.5)
Hyperlipidemia (n, %)	3 (37.5)
Maximum aortic diameter (cm)	6.3 ± 1.697

Data are presented as number (percentage) or mean ± standard deviation. AAA, abdominal aortic aneurysm.

Supplementary Table 3. Primers used in this study.

Gene	Forward primers (5' – 3')	Reverse primers (5' – 3')
Primers used for genotyping		
<i>Pdk4^{fl/fl}</i> F1	CTCCTGGGTCATTAGTGAT TGCAT	AAAGATGATTCTAGCAAGC CACTG
<i>Pdk4^{fl/fl}</i> F2	AGATGGAGCAGCTCAAGTT CTTC	GTGGATTTCGGACCAGTCTG A
<i>Myh11-cre</i>	TGACCCCATCTCTTCACTC C	AGTCCCTCACATCCTCAGG TT
Primers used for RT-PCR		
<i>PDK4</i> (mouse)	AGGGAGGTCGAGCTGTTCT C	GGAGTGTTCACTAAGCGGT CA
<i>PDK4</i> (human)	TTTCCAGACCAACCAATTC ACA	TGCCCCGATTGCATTCTTA
<i>ACTA2</i> (mouse)	GGCATCCACGAAACCACT A	TTCCTGACCACTAGAGGGG G
<i>CNN1</i> (mouse)	GGCAGATCTTTGAGCCAGG T	GGCCCCAAGACTCCAATGA T
<i>SM22α</i> (mouse)	TCCCCAAATATGGAGCCTG T	CACAGCCAAACTGCCCAAA G
<i>KLF4</i> (mouse)	GTGCCCCGACTAACCGTTG	GAGAGGGGACTTGTGACTG C
<i>KLF5</i> (mouse)	CAGGTACGCGCTCTCTTAG G	GGGCATGTCTAGATCCGGT G
<i>Tfam</i> (mouse)	CCGTATTGCGTGAGACGAA C	TCGTTTCACACTTCGACGG A
<i>Tfblm</i> (mouse)	CCCACCATTCGGGAGATCA T	TAGAACCCGCAGCTTTCTG G
<i>Ogdh</i> (mouse)	TGAGAGTTTGGAGCCCGGA	GCAAGATCAAGTTTGTCTG TGGA

<i>Pgclα</i> (mouse)	ATTTCAGCTGCCTTATTGG TTTCG	AGCAGCACACTGGTTGGAA G
<i>Hif1α</i> (mouse)	CTTGACAAGCTAGCCGGAG G	AATATGGCCCGTGCAGTGA A
<i>Slc2a1</i> (mouse)	AGGGCCTAAGGTCACATG AAG	AAACAGCGACACCACAGTG A
<i>Myc</i> (mouse)	GCTTGGCGGGAAAAAGAA GG	CGACCGCAACATAGGATGG A
<i>Pgk1</i> (mouse)	GATGCTTTCCGAGCCTCAC T	TTGGCCAGTCTTGGCATTCT
<i>IL-1β</i> (mouse)	TGCCACCTTTTGACAGTGA TG	TTCTTGTGACCCTGAGCGA C
<i>IL-18</i> (mouse)	CCTTTGAGGCATCCAGGAC A	GTCTGGTCTGGGGTTCACT G
<i>TNF-α</i> (mouse)	ACCCTCACACTCACAAACC A	ACCCTGAGCCATAATCCCC T
<i>IL-6</i> (mouse)	GCCTTCTTGGGACTGATGC T	TGTGACTCCAGCTTATCTCT TGG
<i>β-actin</i> (mouse)	GTTGGAGCAAACATCCCC A	CGCGACCATCCTCCTCTTA G
<i>mtDNA ATP-6</i>	ACCAATAGCCCTGGCCGTA C	GGTGGCGCTTCCAATTAGG T
<i>nDNA GAPDH</i>	CGGGGCTCTCCAGAACATC	ATGACCTTGCCCACAGCCT

Supplementary Table 4. Design of the animal experiments.

Mouse group	substrain	Sex	Age (week)	Number (prior to experiment)	Number (after termination)	Littermates (Yes/No)
wild-type + saline	C57BL/6J	male	8	6	6	No
wild-type + <i>PCSK9</i> ^{DY} /Ang II	C57BL/6J	male	8	6	5	No
PDK4 Wild-type (<i>Pdk4</i> ^{fl/fl}) + <i>PCSK9</i> ^{DY} /Ang II	C57BL/6J	male	8	22	18	No
PDK4 VSMC-knockout (<i>Pdk4</i> ^{SMKO}) + <i>PCSK9</i> ^{DY} /Ang II	C57BL/6J	male	8	22	22	No
wild-type + AAV-NC+ <i>PCSK9</i> ^{DY} /Ang II	C57BL/6J	male	8	21	18	No
wild-type + AAV- <i>PDK4</i> + <i>PCSK9</i> ^{DY} /Ang II	C57BL/6J	male	8	21	12	No
<i>PDK4</i> Wild-type (<i>Pdk4</i> ^{fl/fl}) + <i>PCSK9</i> ^{DY} /Ang II 3d	C57BL/6J	male	8	16	16	No
<i>PDK4</i> VSMC-knockout (<i>Pdk4</i> ^{SMKO}) + <i>PCSK9</i> ^{DY} /Ang II 3d	C57BL/6J	male	8	16	16	No
wild-type + AAV- <i>PCSK9</i> ^{DY} /Ang II + saline	C57BL/6J	male	8	22	16	No
wild-type + AAV-+ <i>PCSK9</i> ^{DY} /Ang II +DCA	C57BL/6J	male	8	22	21	No
wild-type + AAV- <i>PDK4</i> + <i>PCSK9</i> ^{DY} /Ang II + saline	C57BL/6J	male	8	22	13	No
wild-type + AAV- <i>PDK4</i> + <i>PCSK9</i> ^{DY} /Ang II + MCC950	C57BL/6J	male	8	22	20	No

Supplementary Table 5. Gene sets used in this study.

Pathway-related gene sets					
Pyroptosis					
<i>Gsdmd</i>	<i>Adora2a</i>	<i>Adora3</i>	<i>Smim1</i>	<i>Cd274</i>	<i>Icam1</i>
<i>Casp1</i>	<i>Prkaca</i>	<i>Osm</i>	<i>Tet2</i>	<i>Setd7</i>	<i>Stk4</i>
<i>Casp4</i>	<i>Tirap</i>	<i>Pecam1</i>	<i>Ctsl</i>	<i>Fgf21</i>	<i>Gsk3b</i>
<i>Gsdmc4</i>	<i>Trim24</i>	<i>Mettl14</i>	<i>Mlkl</i>	<i>Ikzf1</i>	<i>Ptgs2</i>
<i>Nlrp1b</i>	<i>Naip2</i>	<i>Bak1</i>	<i>Ptpn11</i>	<i>Bsg</i>	<i>Mst1</i>
<i>Il1b</i>	<i>Mefv</i>	<i>Bax</i>	<i>Mapk14</i>	<i>Cebpb</i>	<i>Prfl</i>
<i>Gsdma</i>	<i>Dhx9</i>	<i>Scaf11</i>	<i>Apoe</i>	<i>Tfam</i>	<i>Prmt5</i>
<i>Aim2</i>	<i>Stat3</i>	<i>Gja1</i>	<i>Anxa1</i>	<i>Trim21</i>	<i>Elavl1</i>
<i>Casp8</i>	<i>Sirt1</i>	<i>Snip1</i>	<i>Sdhb</i>	<i>Nlrx1</i>	<i>Mpeg1</i>
<i>Gzma</i>	<i>Ctsg</i>	<i>Prdm1</i>	<i>Chmp2a</i>	<i>Usf2</i>	<i>Abl1</i>
<i>Pycard</i>	<i>Nek7</i>	<i>Vdr</i>	<i>Chmp2b</i>	<i>Slc30a7</i>	<i>Epha2</i>
<i>Il18</i>	<i>Trem2</i>	<i>Ager</i>	<i>Chmp3</i>	<i>Malt1</i>	<i>Hdac6</i>
<i>Zbp1</i>	<i>Foxo3</i>	<i>Ikbke</i>	<i>Chmp4b</i>	<i>Tlr2</i>	<i>Tlr3</i>
<i>Casp3</i>	<i>Trp53</i>	<i>Pkm</i>	<i>Chmp4c</i>	<i>Cycs</i>	<i>Sqstm1</i>
<i>Nlrc4</i>	<i>Nfe2l2</i>	<i>Ifi204</i>	<i>Chmp7</i>	<i>Il1a</i>	<i>Cdk9</i>
<i>Casp6</i>	<i>Txnip</i>	<i>Ifi203</i>	<i>Eef2k</i>	<i>Irf1</i>	<i>Irf3</i>
<i>Zdhc1</i>	<i>Ddx3x</i>	<i>Mndal</i>	<i>Fpr2</i>	<i>Irf2</i>	<i>Ucp1</i>
<i>Pten</i>	<i>Sesn2</i>	<i>Ifi205</i>	<i>Htra1</i>	<i>Trp63</i>	<i>Trem1</i>
<i>Adora1</i>	<i>Elane</i>	<i>Crtac1</i>	<i>Pak2</i>	<i>Casp9</i>	<i>Tslp</i>
<i>Adora2b</i>	<i>Ubr2</i>	<i>Sez6l2</i>	<i>Ndufa13</i>	<i>Gpx4</i>	<i>Il6</i>
<i>Nod2</i>	<i>Plcgl</i>				

OXPHOS					
<i>Cox17</i>	<i>Cox5b</i>	<i>Cox6b1</i>	<i>Cox7a2l</i>	<i>Cox7b</i>	<i>mt-Atp6</i>
<i>mt-Nd2</i>	<i>mt-Nd4</i>	<i>Ndufa4l2</i>	<i>Ndufb3</i>	<i>Ndufb6</i>	<i>Ndufc1</i>
<i>Ndufc2</i>					
ATP.synthesis					
<i>Lrpprc</i>	<i>Etfdh</i>	<i>mt-Nd6</i>	<i>Ndufb10</i>	<i>Atp5f1d</i>	<i>Surf1</i>
<i>Trap1</i>	<i>Tmem186</i>	<i>Ndufa1</i>	<i>Ndufc1</i>	<i>Timmdc1</i>	<i>Ucp1</i>
<i>Atp5pd</i>	<i>Ndufaf3</i>	<i>Ndufa2</i>	<i>Ndufc2</i>	<i>Atp5f1e</i>	<i>Ucp2</i>
<i>Atp5mg</i>	<i>Uqcrq</i>	<i>Ndufa3</i>	<i>Ndufs1</i>	<i>Atp5pb</i>	<i>Ucp3</i>
<i>Uqcr11</i>	<i>Dmac2l</i>	<i>Ndufa4</i>	<i>Ndufs2</i>	<i>Atp5mc1</i>	<i>Uqcrb</i>
<i>Cox20</i>	<i>Cox18</i>	<i>Ndufa5</i>	<i>Ndufs3</i>	<i>Atp5mc2</i>	<i>Uqcrc1</i>
<i>Ndufa11</i>	<i>Acad9</i>	<i>Ndufa6</i>	<i>Ndufv1</i>	<i>Atp5mc3</i>	<i>Uqcrc2</i>
<i>Cox4i1</i>	<i>Ndufaf4</i>	<i>Ndufa7</i>	<i>Ndufs4</i>	<i>Atp5me</i>	<i>Uqcrfs1</i>
<i>Cox5b</i>	<i>Uqcr10</i>	<i>Ndufa8</i>	<i>Ndufs5</i>	<i>Atp5pf</i>	<i>Uqcrh</i>
<i>Cox6a1</i>	<i>Ndufs7</i>	<i>Ndufa9</i>	<i>Ndufs6</i>	<i>Atp5po</i>	<i>Ndufaf5</i>
<i>Cox6b1</i>	<i>mt-Atp6</i>	<i>Ndufa10</i>	<i>Ndufs8</i>	<i>Cycs</i>	<i>Coq10b</i>
<i>Cox6c</i>	<i>mt-Atp8</i>	<i>Ndufab1</i>	<i>Ndufv2</i>	<i>Ndufb11</i>	<i>Nubpl</i>
<i>Cox7b</i>	<i>mt-Co1</i>	<i>Ndufb1</i>	<i>Ndufv3</i>	<i>Ndufaf7</i>	<i>Cox14</i>
<i>Cox7c</i>	<i>mt-Co2</i>	<i>Ndufb2</i>	<i>Atp5f1a</i>	<i>Coal</i>	<i>Slc25a14</i>
<i>Cox8a</i>	<i>mt-Co3</i>	<i>Ndufb3</i>	<i>Atp5f1b</i>	<i>Tmem126b</i>	<i>Cox19</i>
<i>Cox11</i>	<i>mt-Cyb</i>	<i>Ndufb4</i>	<i>Atp5f1c</i>	<i>Ndufa12</i>	<i>Cox7a2l</i>
<i>Ndufaf6</i>	<i>mt-Nd1</i>	<i>Ndufb5</i>	<i>Ndufa13</i>	<i>Sco1</i>	<i>Ndufaf2</i>
<i>Pm20d1</i>	<i>mt-Nd2</i>	<i>Ndufb6</i>	<i>Ndufaf1</i>	<i>Sdha</i>	<i>Coq10a</i>
<i>Cyc1</i>	<i>mt-Nd3</i>	<i>Ndufb7</i>	<i>Taco1</i>	<i>Sdhb</i>	<i>Cox5a</i>

<i>Etfa</i>	<i>mt-Nd4</i>	<i>Ndufb8</i>	<i>Cox16</i>	<i>Sdhc</i>	<i>Slc25a27</i>
<i>Etfb</i>	<i>mt-Nd5</i>	<i>Ndufb9</i>	<i>Ecsit</i>	<i>Sdhd</i>	<i>Atp5mf</i>
<i>Sco2</i>					
Complex.I					
<i>Ndufaf6</i>	<i>mt-Nd5</i>	<i>Ndufa10</i>	<i>Ndufb8</i>	<i>Ndufs4</i>	<i>Ndufb11</i>
<i>Tmem186</i>	<i>mt-Nd6</i>	<i>Ndufab1</i>	<i>Ndufb9</i>	<i>Ndufs5</i>	<i>Tmem70</i>
<i>Ndufaf3</i>	<i>Ndufa1</i>	<i>Ndufb1</i>	<i>Ndufb10</i>	<i>Ndufs6</i>	<i>Dmac2</i>
<i>Acad9</i>	<i>Ndufa2</i>	<i>Ndufb2</i>	<i>Ndufc1</i>	<i>Ndufv2</i>	<i>Ndufaf7</i>
<i>Ndufaf4</i>	<i>Ndufa3</i>	<i>Ndufb3</i>	<i>Ndufc2</i>	<i>Ndufv3</i>	<i>Foxred1</i>
<i>mt-Nd1</i>	<i>Ndufa5</i>	<i>Ndufb4</i>	<i>Ndufs1</i>	<i>Ndufa13</i>	<i>Coa1</i>
<i>mt-Nd2</i>	<i>Ndufa6</i>	<i>Ndufb5</i>	<i>Ndufs2</i>	<i>Ndufaf1</i>	<i>Tmem126b</i>
<i>mt-Nd4</i>	<i>Ndufa7</i>	<i>Ndufb6</i>	<i>Ndufs3</i>	<i>Ecsit</i>	<i>Ndufa12</i>
<i>mt-Nd4l</i>	<i>Ndufa8</i>	<i>Ndufb7</i>	<i>Ndufv1</i>	<i>Timmdc1</i>	<i>Nubpl</i>
<i>Dmac1</i>	<i>Ndufaf2</i>				
Complex.II					
<i>Sdhaf4</i>	<i>Sdhaf2</i>	<i>Sdhaf3</i>	<i>Sdha</i>	<i>Sdhb</i>	<i>Sdhc</i>
<i>Sdhd</i>	<i>Sdhaf1</i>				
Complex.III					
<i>Uqcr11</i>	<i>Cyc1</i>	<i>Uqcrq</i>	<i>Uqcr10</i>	<i>mt-Cyb</i>	<i>Ttc19</i>
<i>Uqcc1</i>	<i>Bcs1l</i>	<i>Uqcrb</i>	<i>Uqcrc1</i>	<i>Uqcrc2</i>	<i>Uqcrfs1</i>
<i>Uqcrh</i>	<i>Uqcc3</i>	<i>Uqcc2</i>	<i>Lym7</i>		
Complex.IV					
<i>Pet100</i>	<i>Cox6a1</i>	<i>Cox8a</i>	<i>Higd1a</i>	<i>mt-Co2</i>	<i>Tmem177</i>
<i>Pet117</i>	<i>Cox6b1</i>	<i>Cox10</i>	<i>Cox18</i>	<i>mt-Co3</i>	<i>Cox14</i>

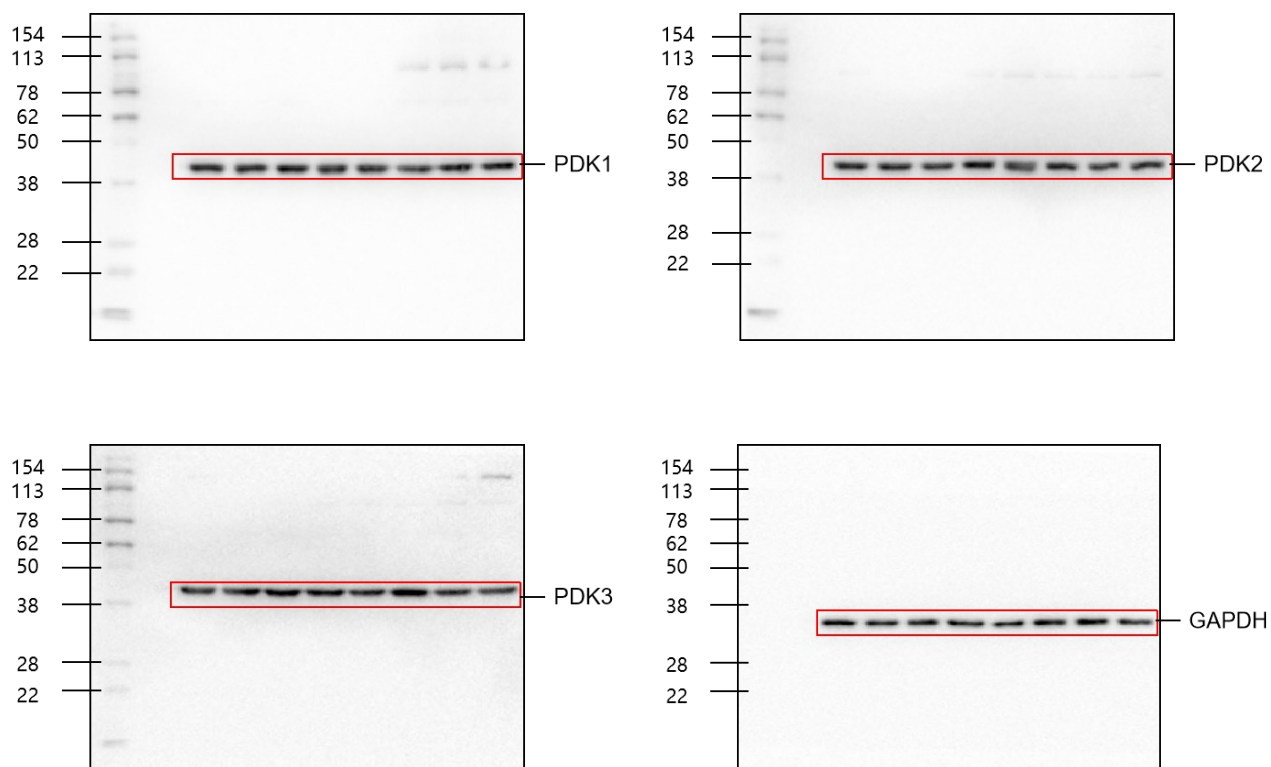
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<i>Cox20</i>	<i>Cox7a2</i>	<i>Cox15</i>	<i>Coa6</i>	<i>Taco1</i>	<i>Cox5a</i>
<i>Cox4i1</i>	<i>Cox7b</i>	<i>Cmc1</i>	<i>Smim20</i>	<i>Cox16</i>	<i>Sco2</i>
<i>Cox5b</i>	<i>Cox7c</i>	<i>Pnkd</i>	<i>mt-Co1</i>	<i>Surf1</i>	
Glycolysis					
<i>Abcb6</i>	<i>Cyb5a</i>	<i>Hs2st1</i>	<i>Pkm</i>	<i>Acss1</i>	<i>Nup160</i>
<i>Adora2b</i>	<i>Dcn</i>	<i>Hs6st2</i>	<i>Pkp2</i>	<i>Acss2</i>	<i>Nup188</i>
<i>Agl</i>	<i>Ddit4</i>	<i>Hspa5</i>	<i>Plod1</i>	<i>Adh1</i>	<i>Nup205</i>
<i>Agrn</i>	<i>Depdc1a</i>	<i>Idh1</i>	<i>Plod2</i>	<i>Adh4</i>	<i>Nup210</i>
<i>Ak3</i>	<i>Dld</i>	<i>Idua</i>	<i>Pmm2</i>	<i>Adh5</i>	<i>Nup214</i>
<i>Ak4</i>	<i>Dpysl4</i>	<i>Ier3</i>	<i>Polr3k</i>	<i>Adh7</i>	<i>Nup35</i>
<i>Akr1a1</i>	<i>Dsc2</i>	<i>Igfbp3</i>	<i>Ppfia4</i>	<i>Aldh1a3</i>	<i>Nup37</i>
<i>Aldh7a1</i>	<i>Ecd</i>	<i>Il13ra1</i>	<i>Ppia</i>	<i>Aldh1b1</i>	<i>Nup12</i>
<i>Aldh9a1</i>	<i>Efna3</i>	<i>Irs2</i>	<i>Ppp2cb</i>	<i>Aldh2</i>	<i>Nup43</i>
<i>Aldoa</i>	<i>Egfr</i>	<i>Isg20</i>	<i>Prps1</i>	<i>Aldh3a1</i>	<i>Nup50</i>
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<i>Alg1</i>	<i>Elf3</i>	<i>Kif20a</i>	<i>Pygb</i>	<i>Aldh3b1</i>	<i>Nup11</i>
<i>Ang</i>	<i>Eno1</i>	<i>Kif2a</i>	<i>Pygl</i>	<i>Aldh3b3</i>	<i>Nup62</i>
<i>Angptl4</i>	<i>Eno2</i>	<i>Lct</i>	<i>Qsox1</i>	<i>Aldoc</i>	<i>Nup85</i>
<i>Ankzf1</i>	<i>Erola</i>	<i>Ldha</i>	<i>Rars</i>	<i>Bpgm</i>	<i>Nup88</i>
<i>Arpp19</i>	<i>Ext1</i>	<i>Ldhc</i>	<i>Rbck1</i>	<i>Dlat</i>	<i>Nup93</i>
<i>Artn</i>	<i>Ext2</i>	<i>Lhpp</i>	<i>Rpe</i>	<i>Eno3</i>	<i>Nup98</i>
<i>Aurka</i>	<i>Fam162a</i>	<i>Lhx9</i>	<i>Rragd</i>	<i>Fbp1</i>	<i>Pfkfb3</i>
<i>B3galt6</i>	<i>Fbp2</i>	<i>Mdh1</i>	<i>Sap30</i>	<i>G6pc</i>	<i>Pfkfb4</i>

<i>B3gat1</i>	<i>Fkbp4</i>	<i>Mdh2</i>	<i>Sdc1</i>	<i>G6pc2</i>	<i>Pgm2l1</i>
<i>B3gat3</i>	<i>Fut8</i>	<i>Me1</i>	<i>Sdc2</i>	<i>Galm</i>	<i>Pgp</i>
<i>B3gnt3</i>	<i>G6pdx</i>	<i>Me2</i>	<i>Sdc3</i>	<i>Gapdh</i>	<i>Pom121</i>
<i>B4galt1</i>	<i>Gal3st1</i>	<i>Med24</i>	<i>Sdhc</i>	<i>Gck</i>	<i>Ppp2ca</i>
<i>B4galt2</i>	<i>Gale</i>	<i>Mertk</i>	<i>Slc16a3</i>	<i>Gpi1</i>	<i>Ppp2r1a</i>
<i>B4galt4</i>	<i>Galk1</i>	<i>Met</i>	<i>Slc25a10</i>	<i>Hk1</i>	<i>Ppp2r1b</i>
<i>B4galt7</i>	<i>Galk2</i>	<i>Mif</i>	<i>Slc25a13</i>	<i>Hk3</i>	<i>Ppp2r5d</i>
<i>Bik</i>	<i>Gapdhs</i>	<i>Miox</i>	<i>Slc35a3</i>	<i>Ldhal6b</i>	<i>Prkaca</i>
<i>Bpnt1</i>	<i>Gclc</i>	<i>Mpi</i>	<i>Slc37a4</i>	<i>Ldhb</i>	<i>Prkacb</i>
<i>Cacna1h</i>	<i>Gfpt1</i>	<i>Mxi1</i>	<i>Sod1</i>	<i>Pck1</i>	<i>Rae1</i>
<i>Capn5</i>	<i>Gfus</i>	<i>Nanp</i>	<i>Sox9</i>	<i>Pck2</i>	<i>Ranbp2</i>
<i>Casp6</i>	<i>Glce</i>	<i>Nasp</i>	<i>Spag4</i>	<i>Pdha1</i>	<i>Sec13</i>
<i>Cd44</i>	<i>GlrX</i>	<i>Ndst3</i>	<i>Srd5a3</i>	<i>Pdha2</i>	<i>Seh1l</i>
<i>Cdk1</i>	<i>Gmppa</i>	<i>Ndufv3</i>	<i>Stc1</i>	<i>Pdhb</i>	<i>Tpr</i>
<i>Cenpa</i>	<i>Gmppb</i>	<i>Nol3</i>	<i>Stc2</i>	<i>Pfkl</i>	<i>Slc2a1</i>
<i>Chpf</i>	<i>Gne</i>	<i>Nsdhl</i>	<i>Stmn1</i>	<i>Pfkm</i>	<i>Mpc1</i>
<i>Chpf2</i>	<i>Gnpda1</i>	<i>Nt5e</i>	<i>Taldo1</i>	<i>Pgk2</i>	<i>Mpc2</i>
<i>Chst1</i>	<i>Got1</i>	<i>P4ha1</i>	<i>Tff3</i>	<i>Pgm1</i>	<i>Slc2a2</i>
<i>Chst12</i>	<i>Got2</i>	<i>P4ha2</i>	<i>Tgfa</i>	<i>Pklr</i>	<i>Slc2a3</i>
<i>Chst2</i>	<i>Gpc1</i>	<i>Pam</i>	<i>Tgfbi</i>	<i>Bid</i>	<i>Slc2a4</i>
<i>Chst4</i>	<i>Gpc3</i>	<i>Paxip1</i>	<i>Tktl1</i>	<i>Cd4</i>	<i>Slc2a5</i>
<i>Chst5</i>	<i>Gpc4</i>	<i>Pcx</i>	<i>Tpbg</i>	<i>Pfkfb2</i>	<i>Prkaa1</i>
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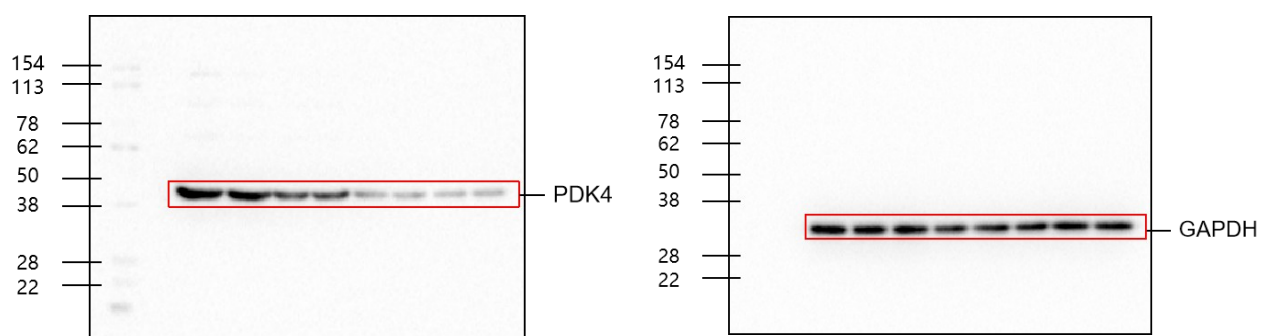
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<i>Cog2</i>	<i>Hax1</i>	<i>Pgam2</i>	<i>Vcan</i>	<i>Ndc1</i>	<i>Hif1a</i>
<i>Col5a1</i>	<i>Hdlbp</i>	<i>Pgk1</i>	<i>Vegfa</i>	<i>Nup107</i>	<i>Pparg</i>
<i>Copb2</i>	<i>Hk2</i>	<i>Pgls</i>	<i>Vldlr</i>	<i>Nup133</i>	
<i>Cth</i>	<i>Hmmr</i>	<i>Pgm2</i>	<i>Xylt2</i>	<i>Nup153</i>	
<i>Cxcr4</i>	<i>Homer1</i>	<i>Phka2</i>	<i>Zfp292</i>	<i>Nup155</i>	

Uncropped Western blot images

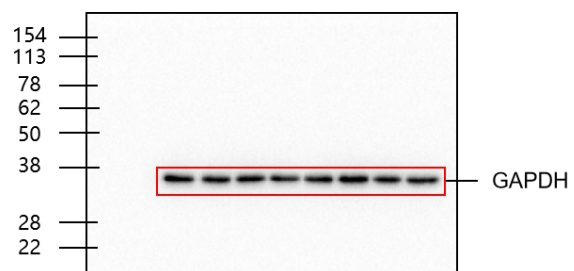
Supplementary Figure 1G



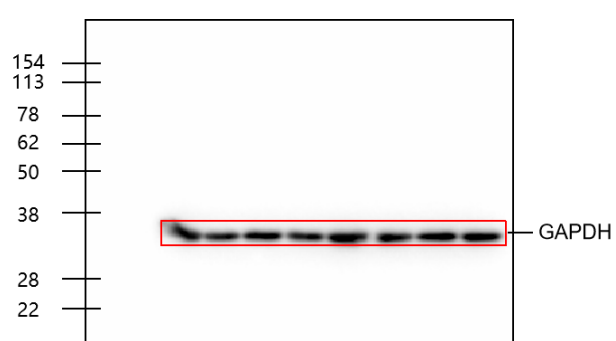
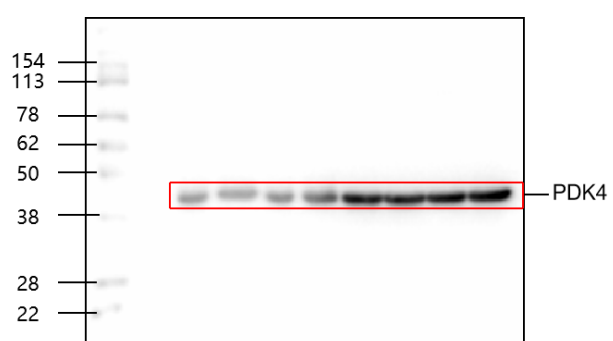
Supplementary Figure 1H



Supplementary Figure 2C



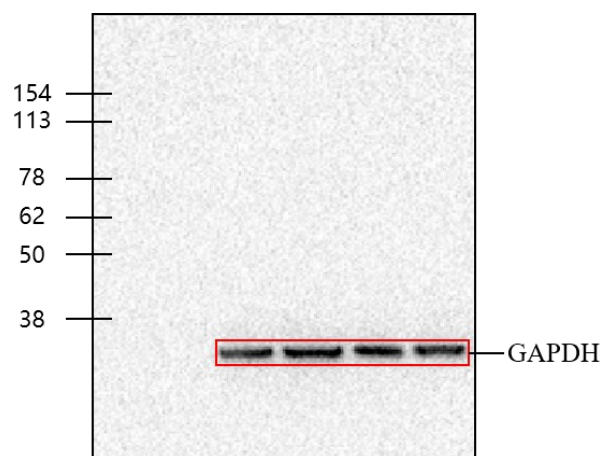
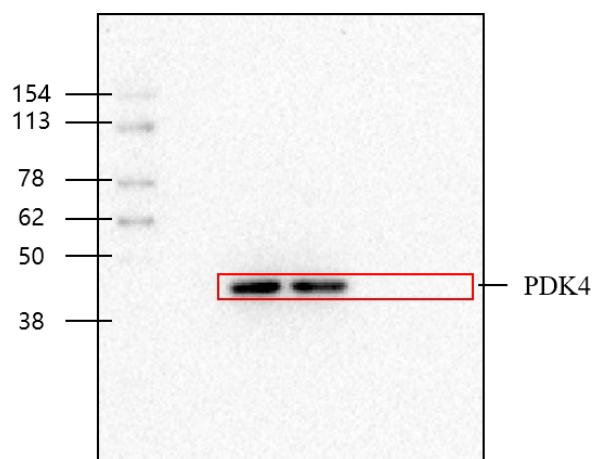
Supplementary Figure 2E



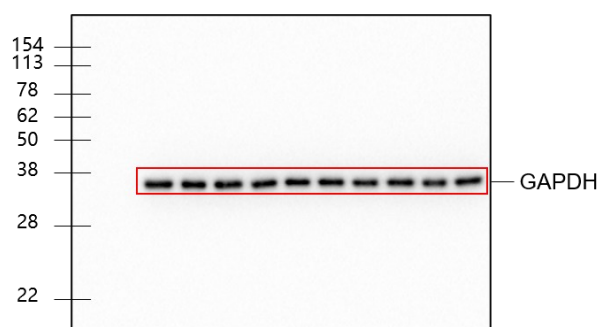
Supplementary Figure 2H



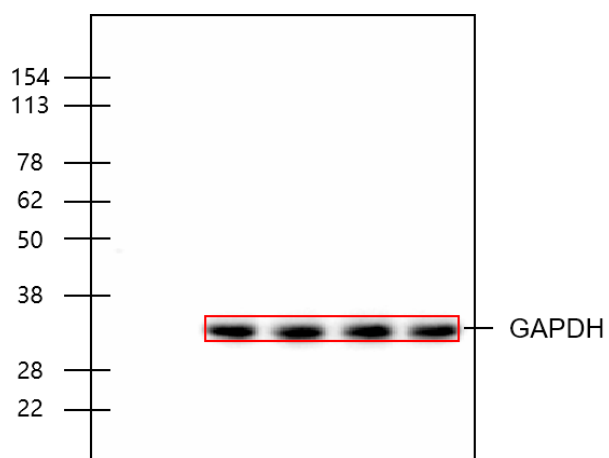
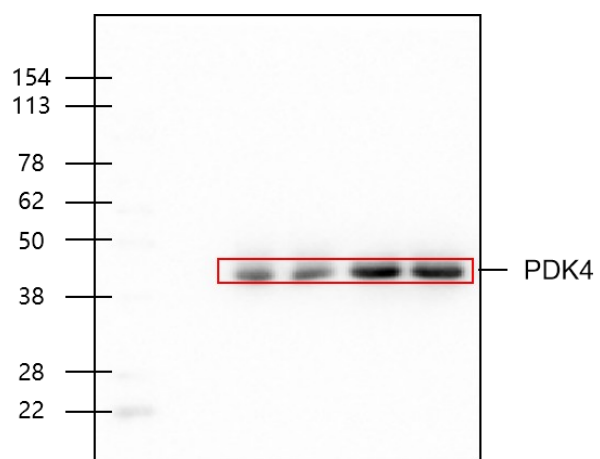
Supplementary Figure 3C



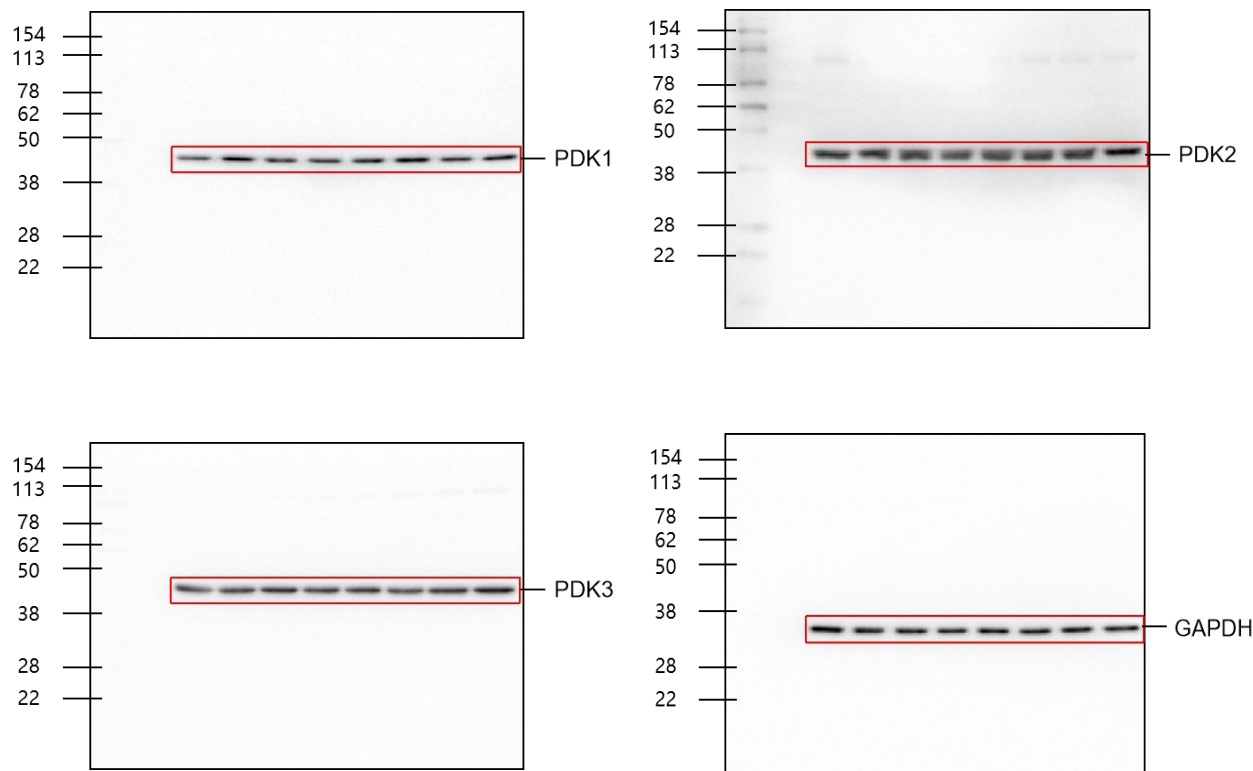
Supplementary Figure 4B



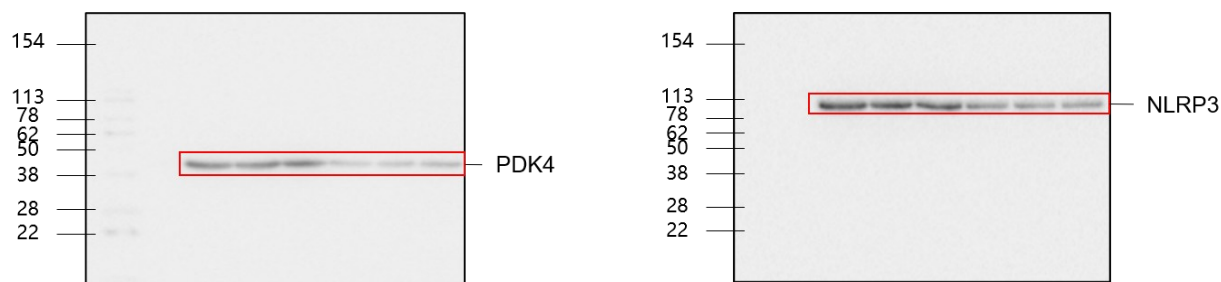
Supplementary Figure 4D

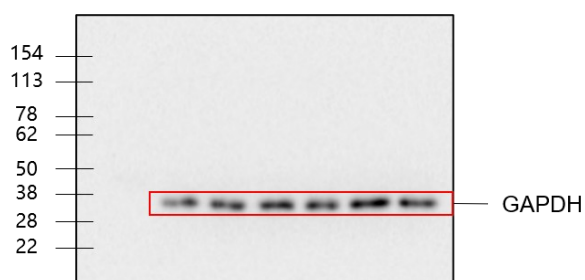
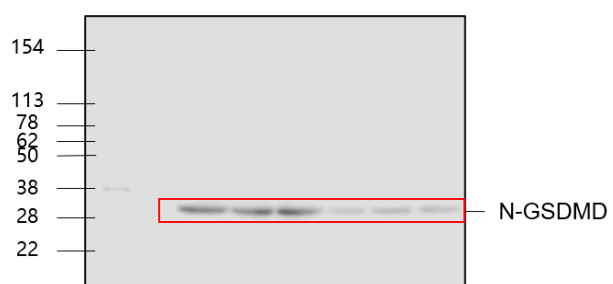
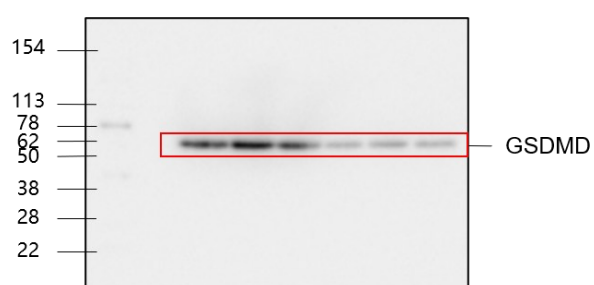
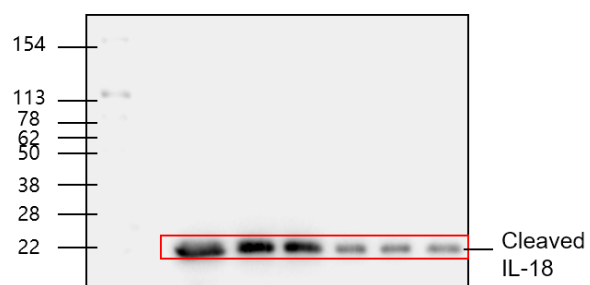
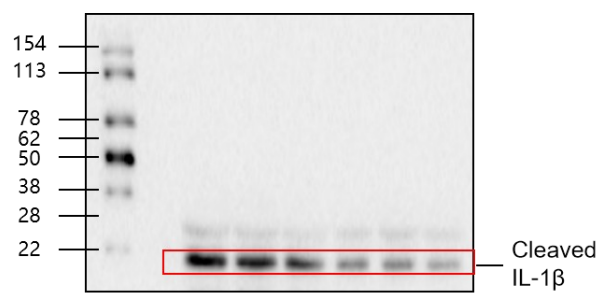


Supplementary Figure 5J

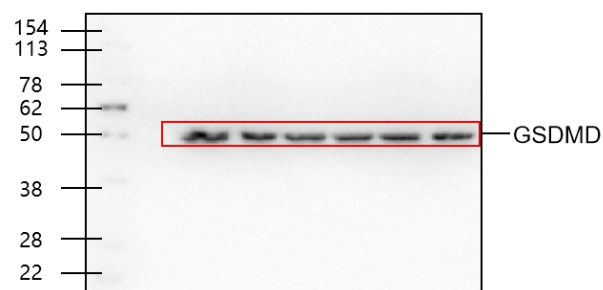
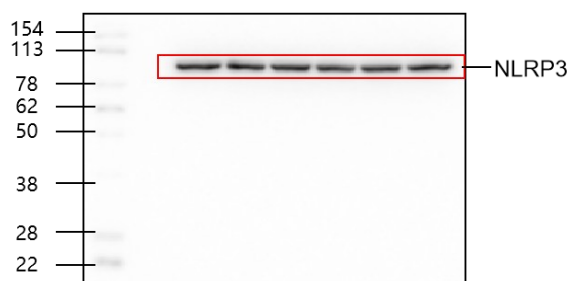


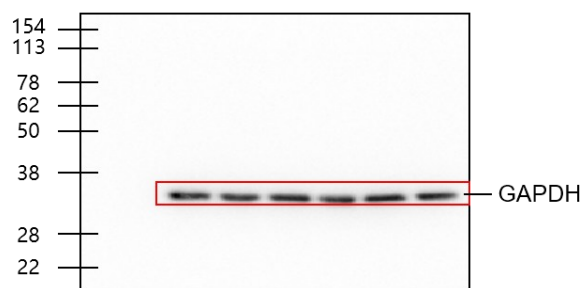
Supplementary Figure 6G



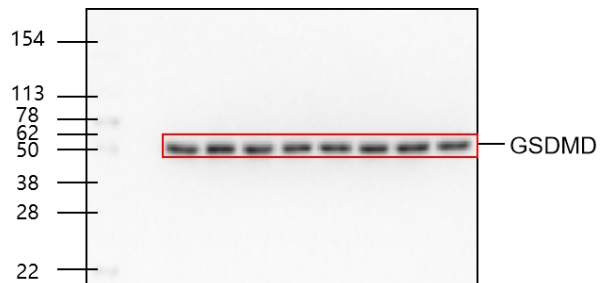
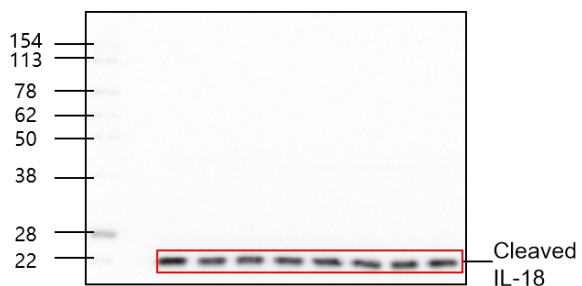
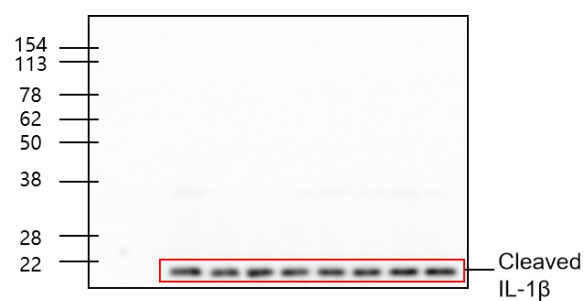
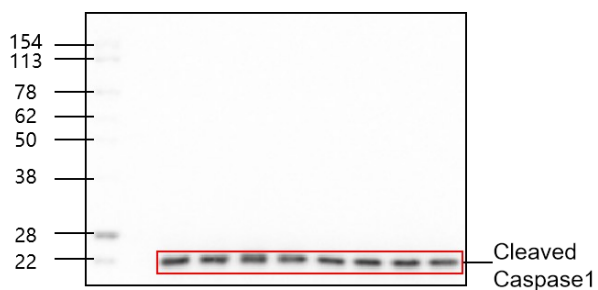
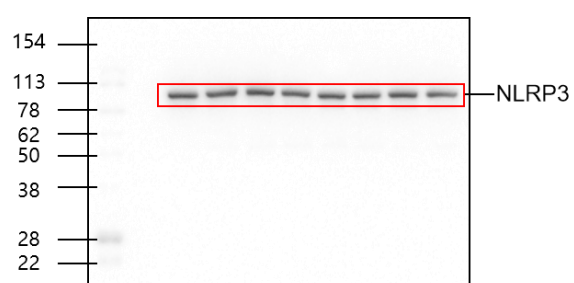
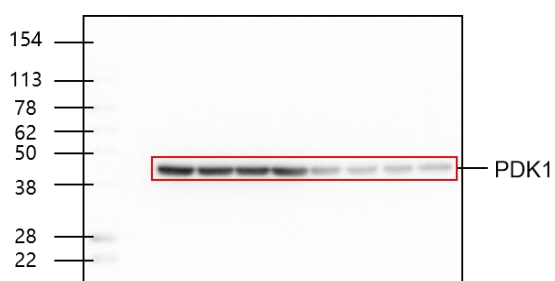


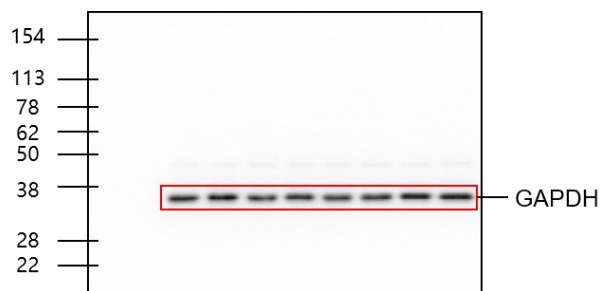
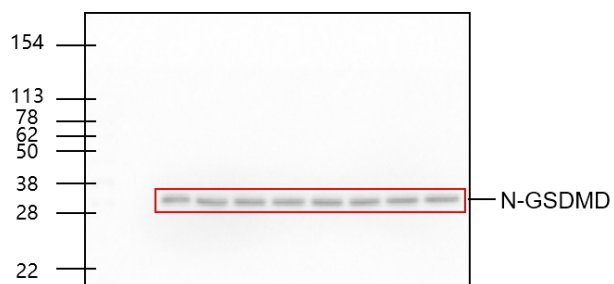
Supplementary Figure 6H



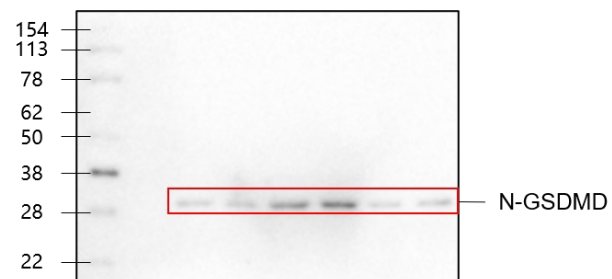
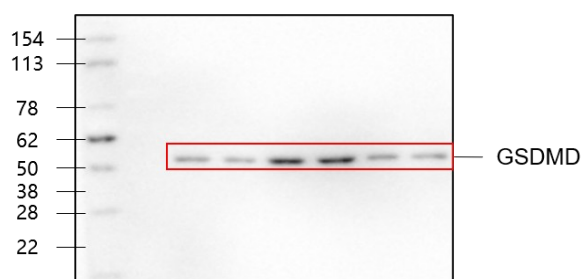
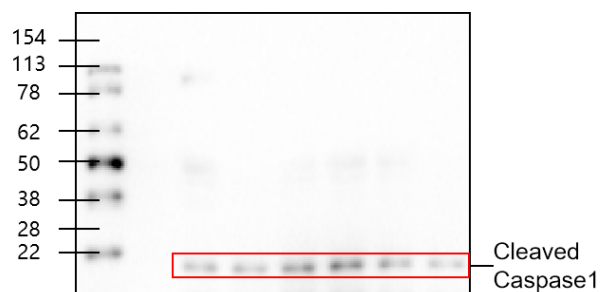


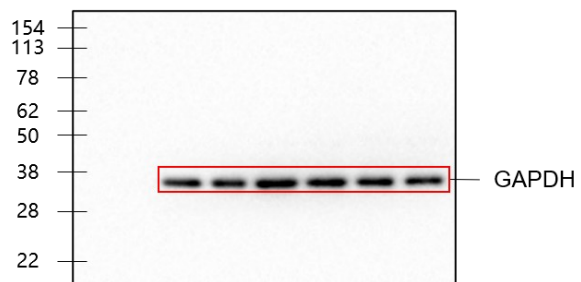
Supplementary Figure 6I



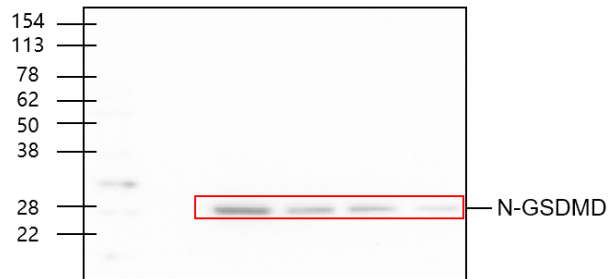
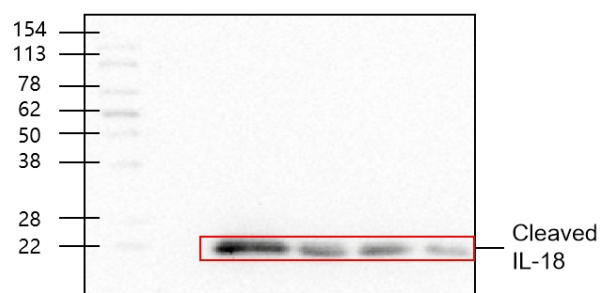
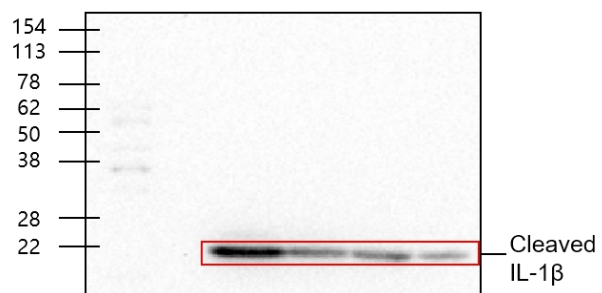
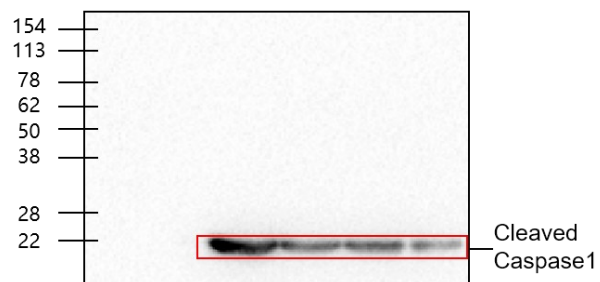
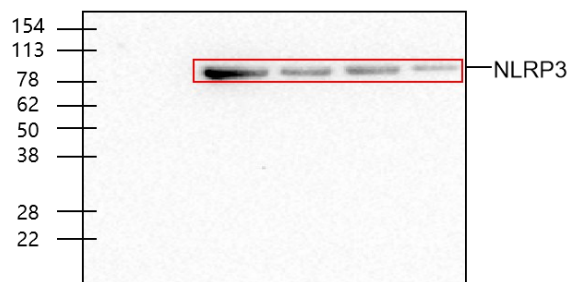


Supplementary Figure 7A



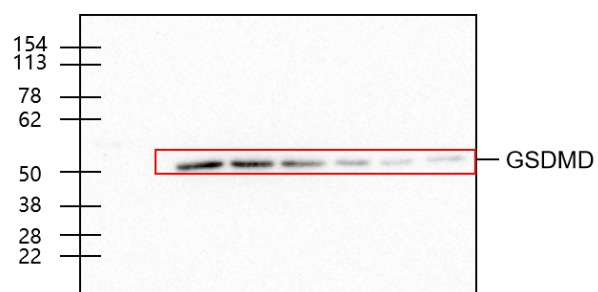
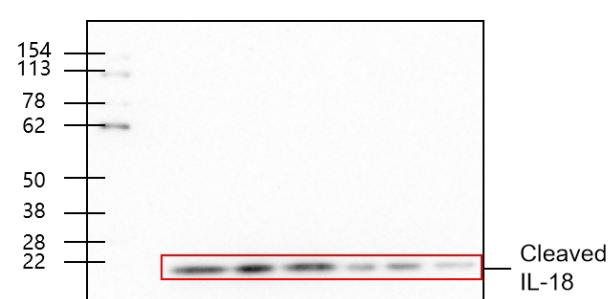
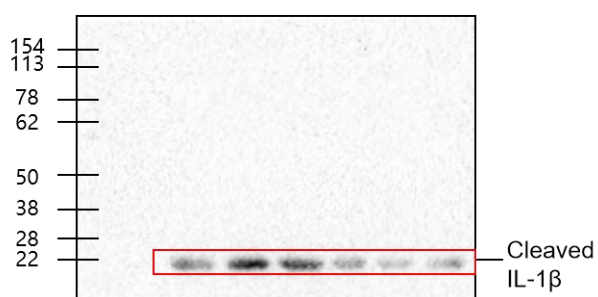
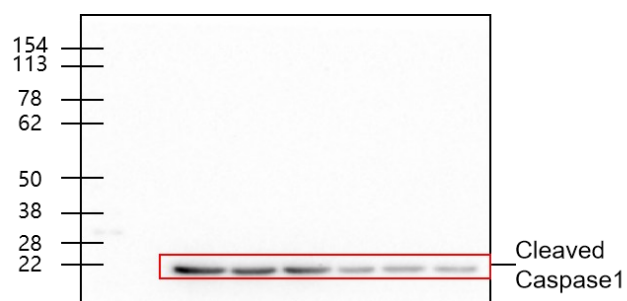
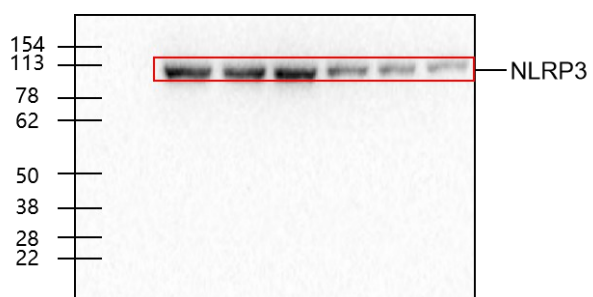


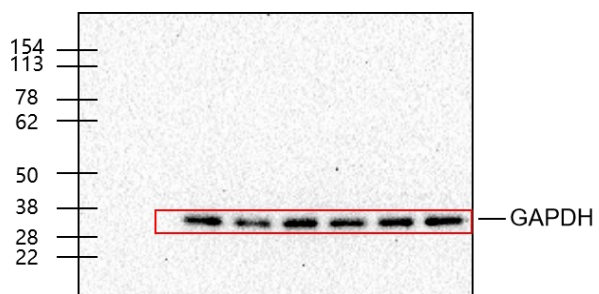
Supplementary Figure 7B



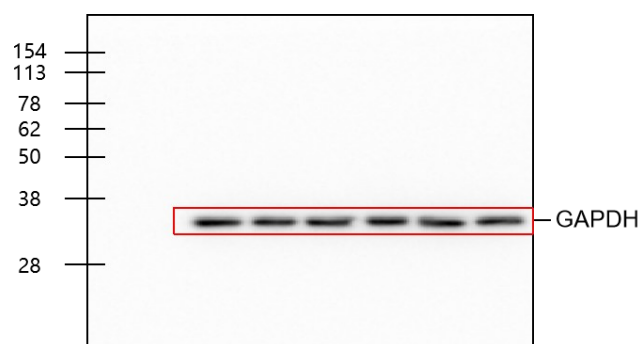
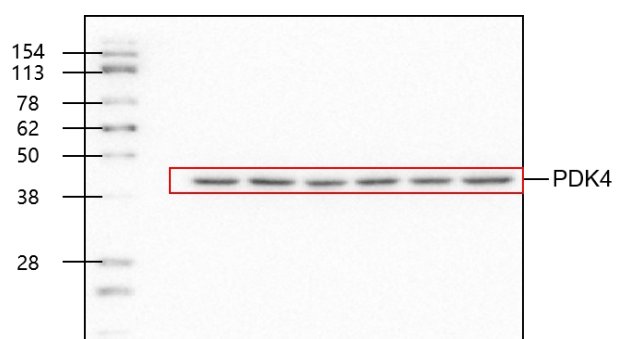


Supplementary Figure 9F





Supplementary Figure 9J



Supplementary Figure 9K

