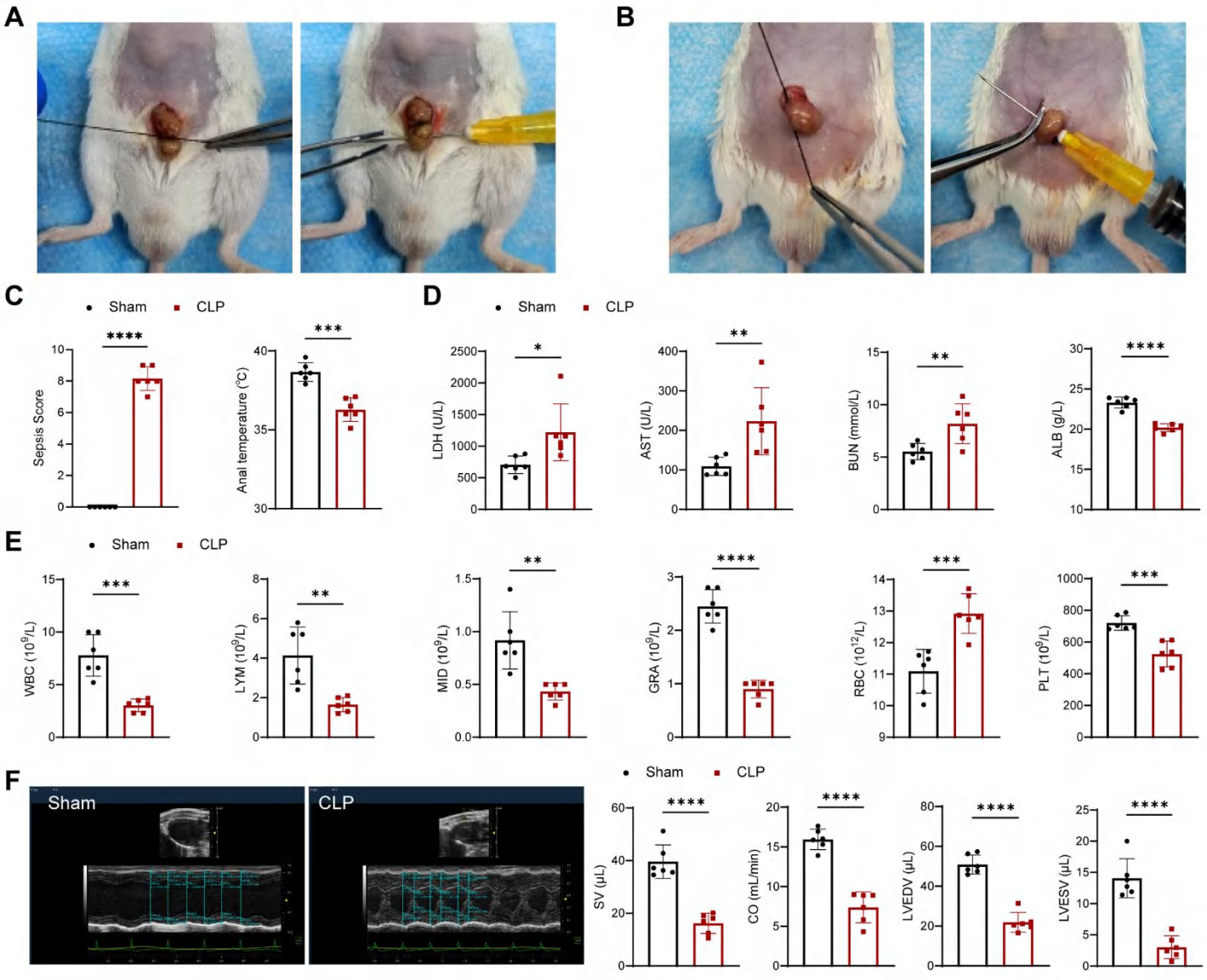
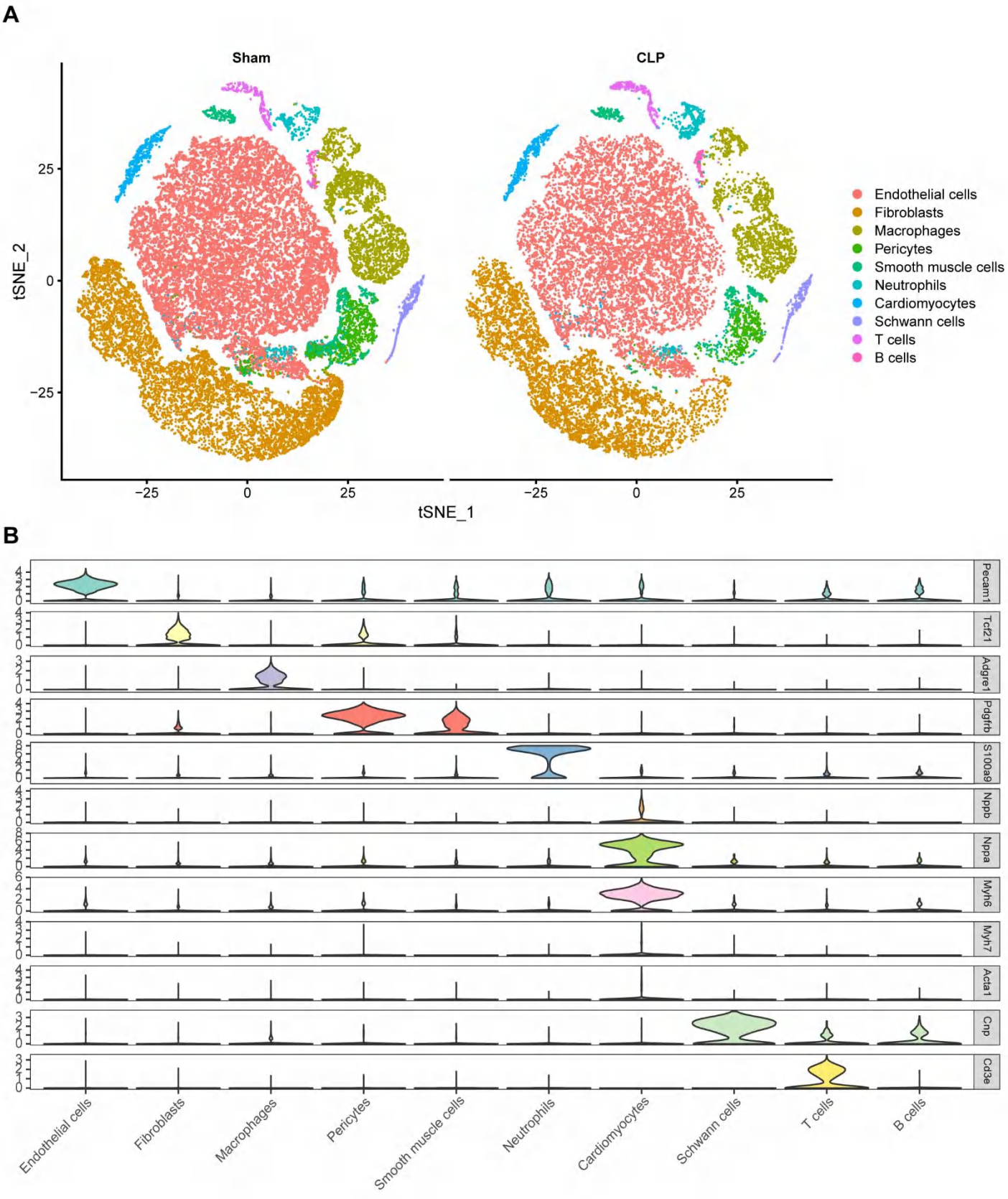
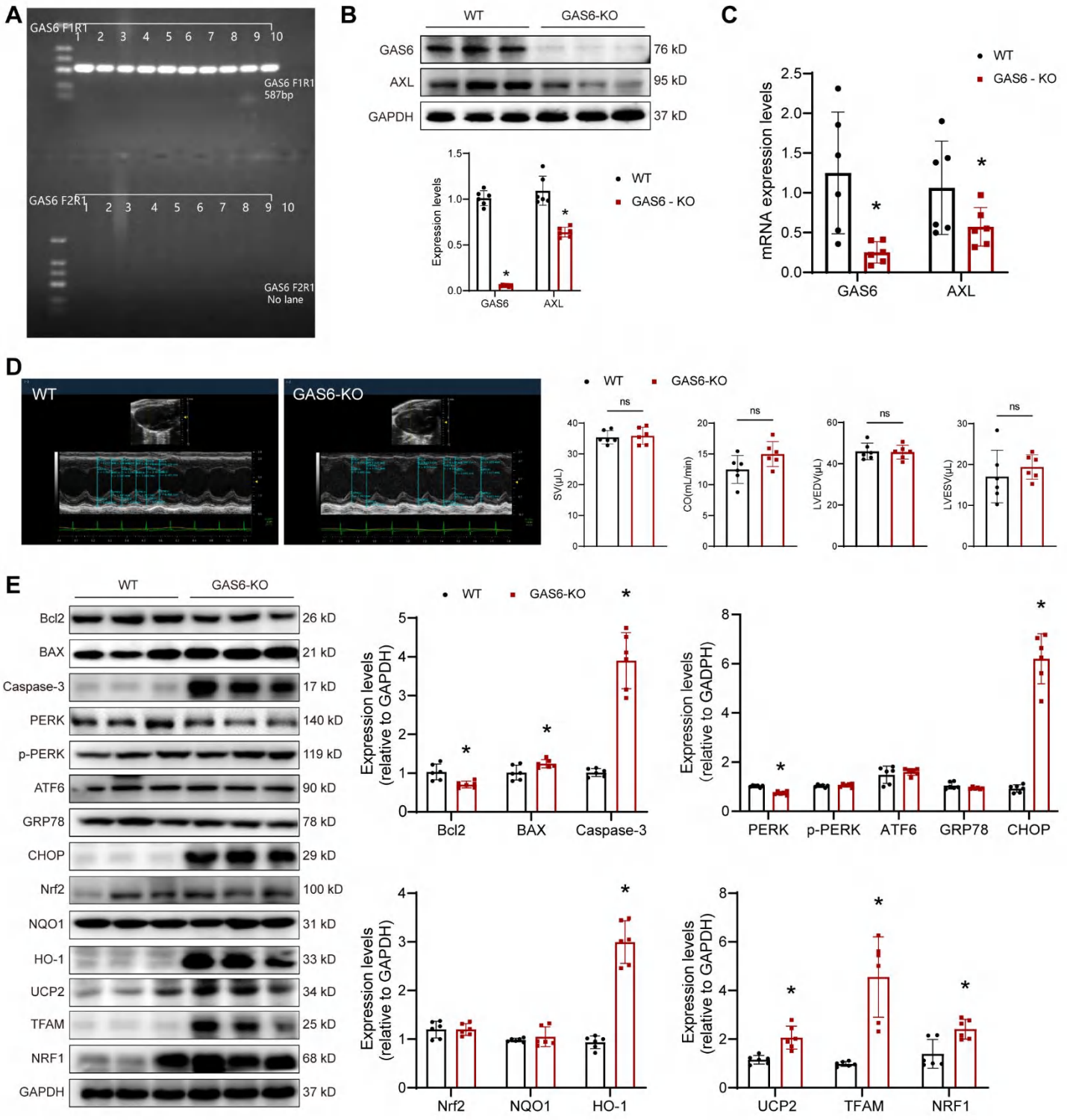
Supplementary Figure 1



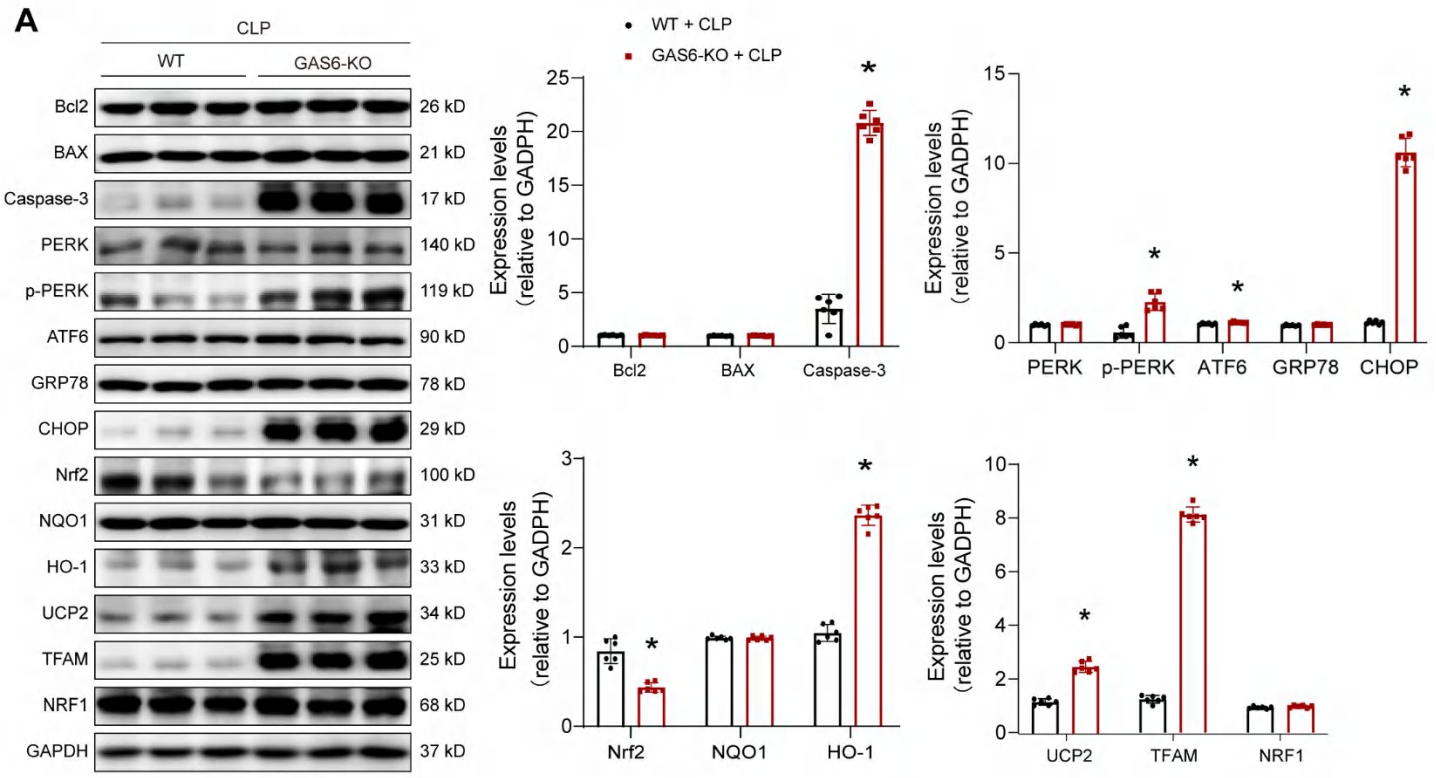
Supplementary Figure 2



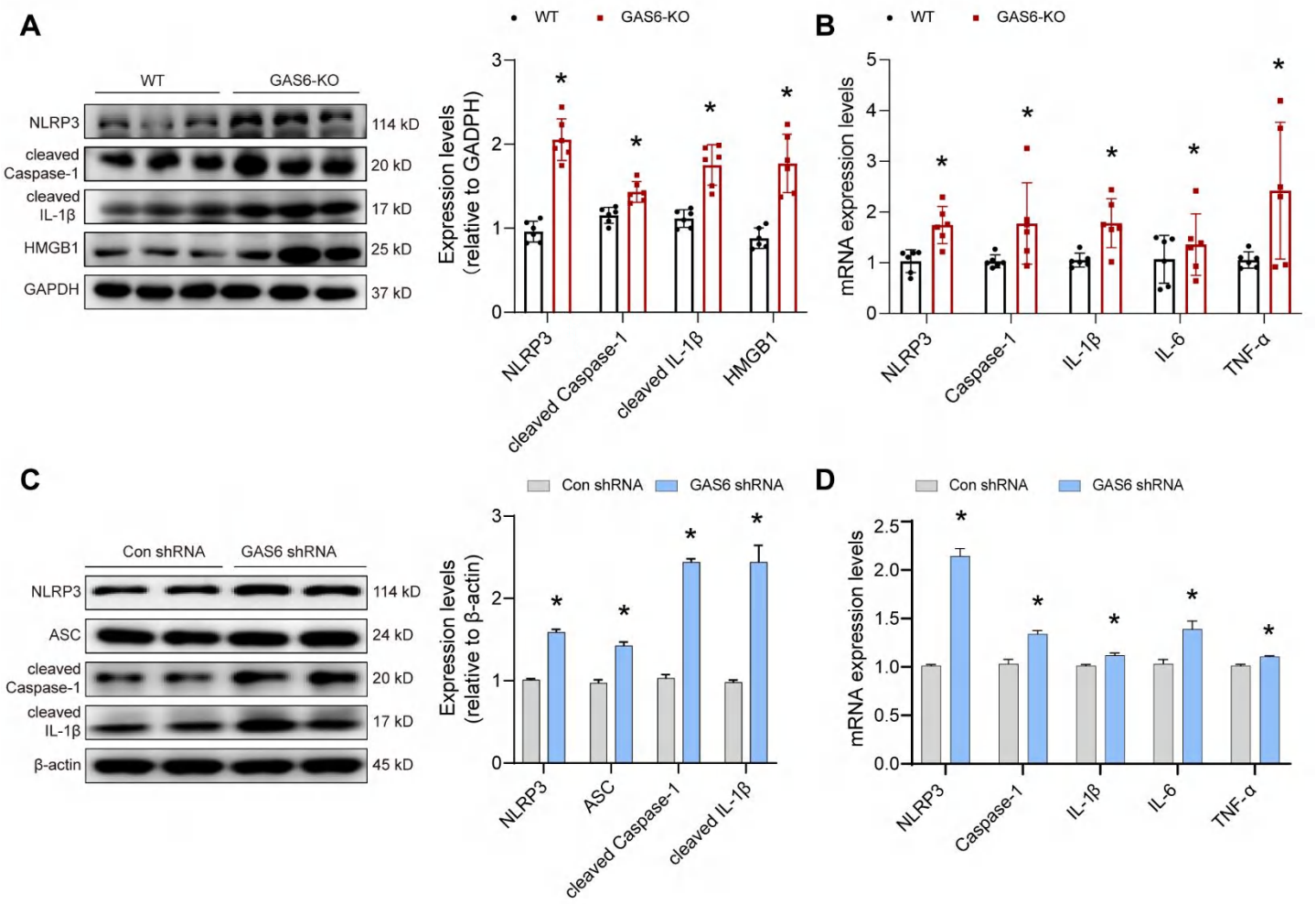
Supplementary Figure 3



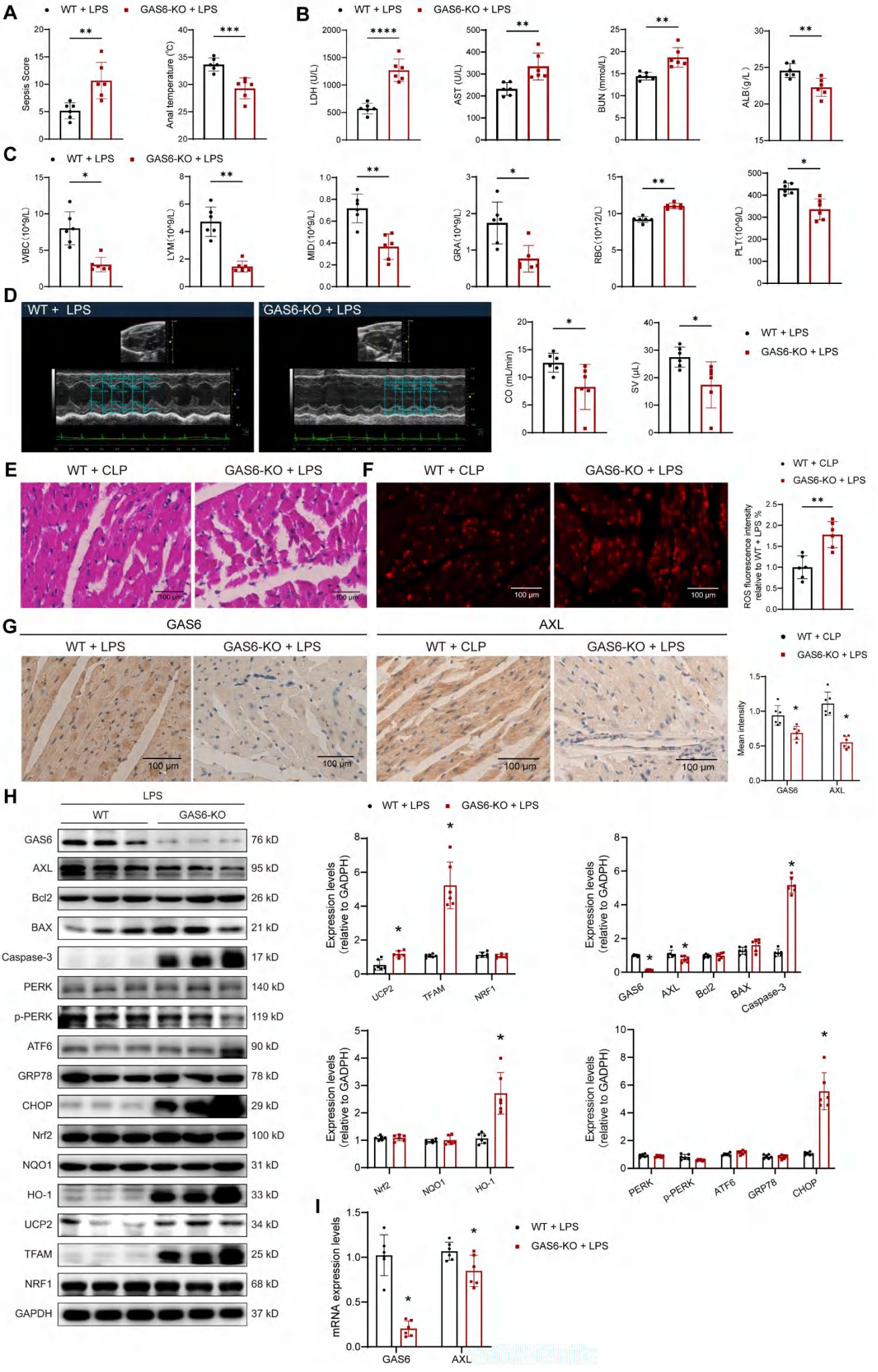
Supplementary Figure 4



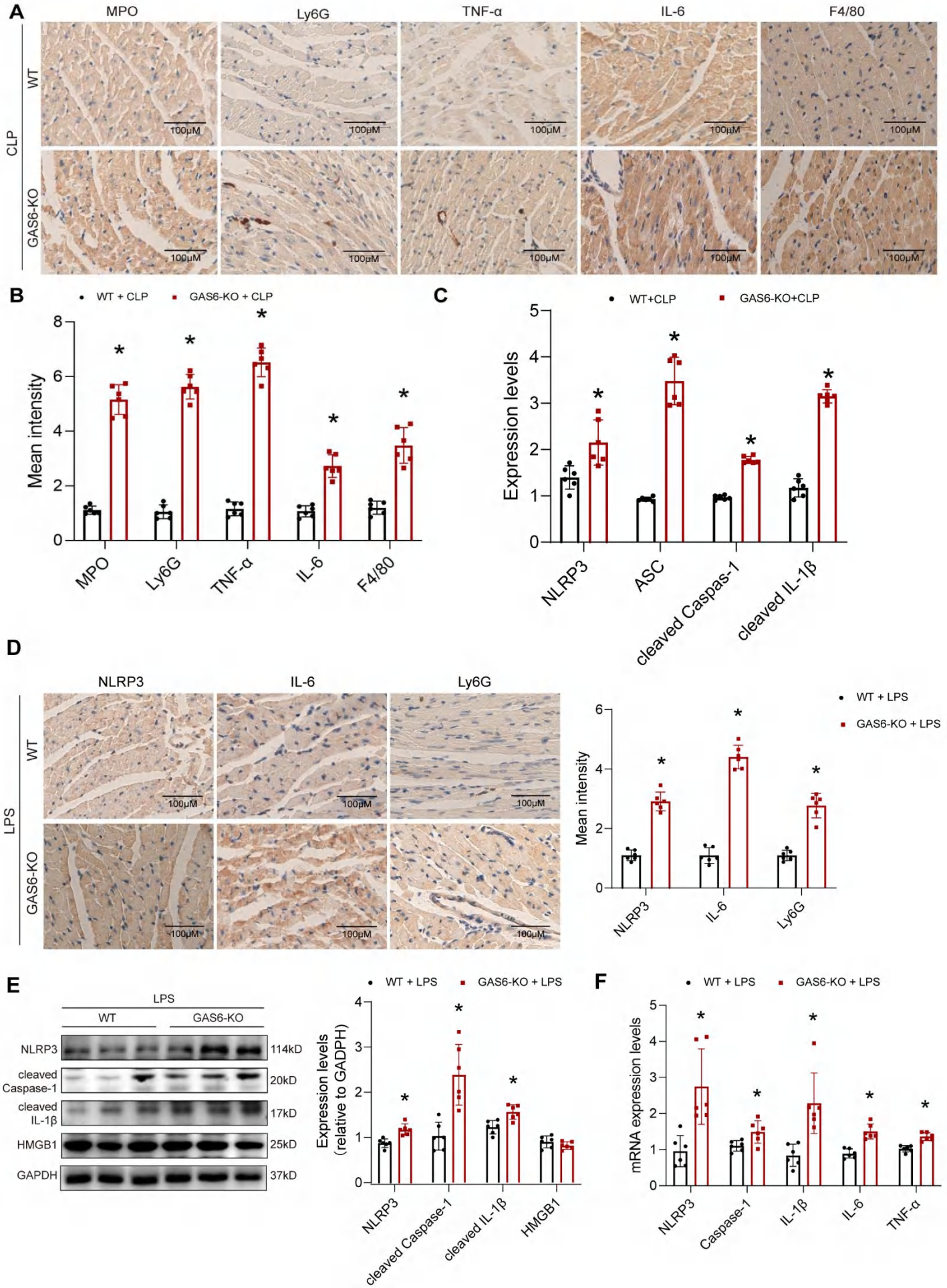
Supplementary Figure 10



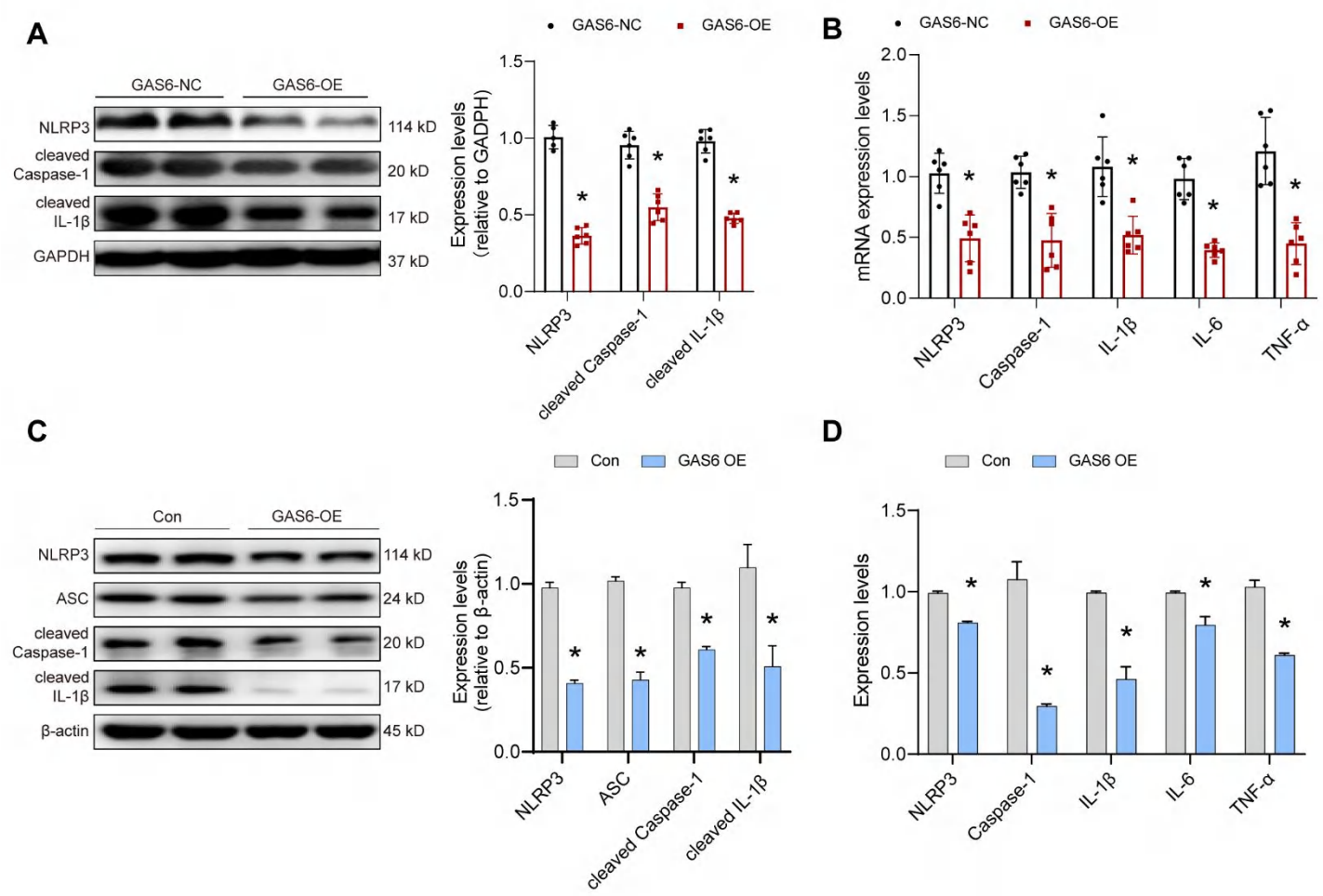
Supplementary Figure 5



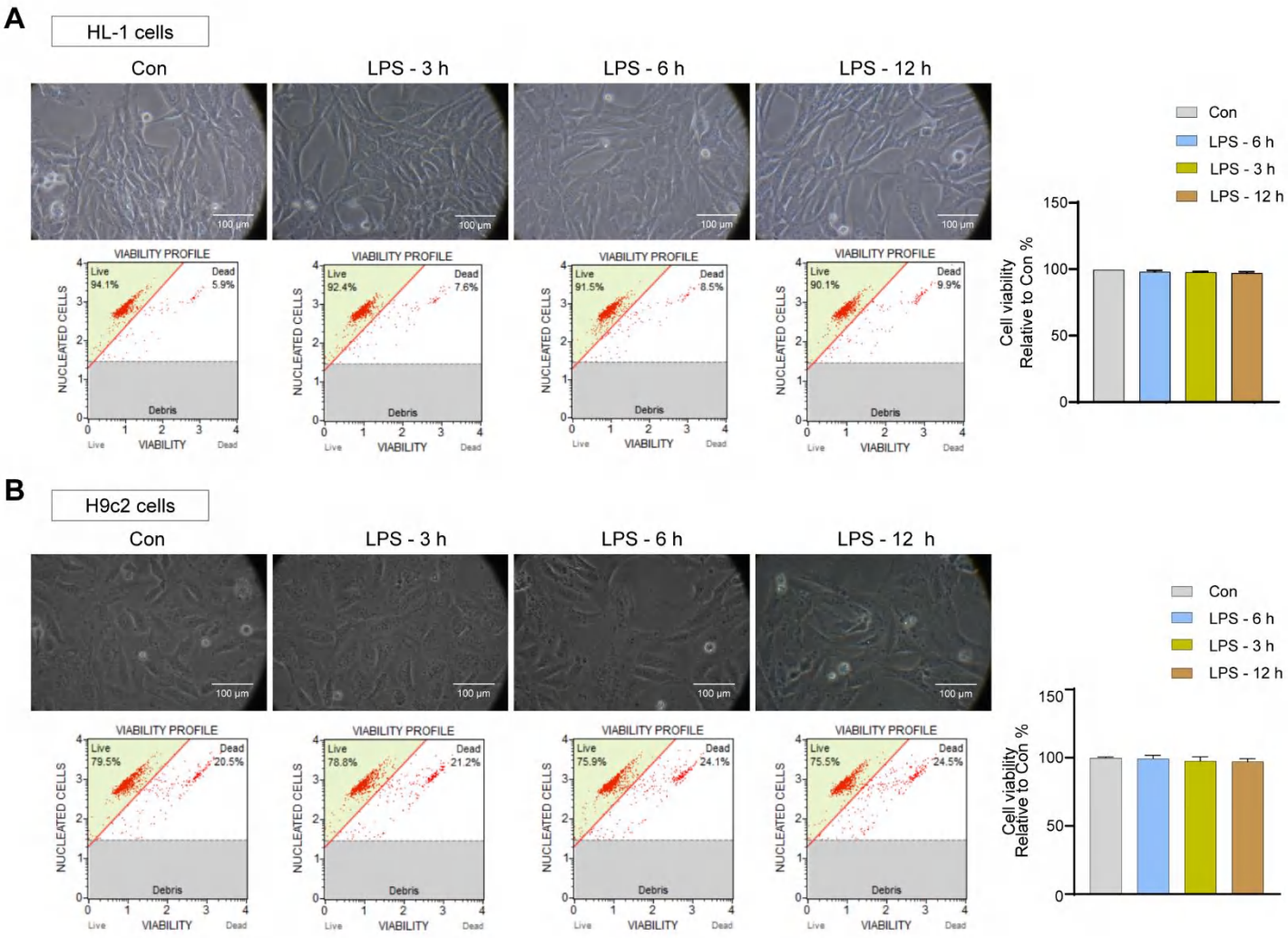
Supplementary Figure 11



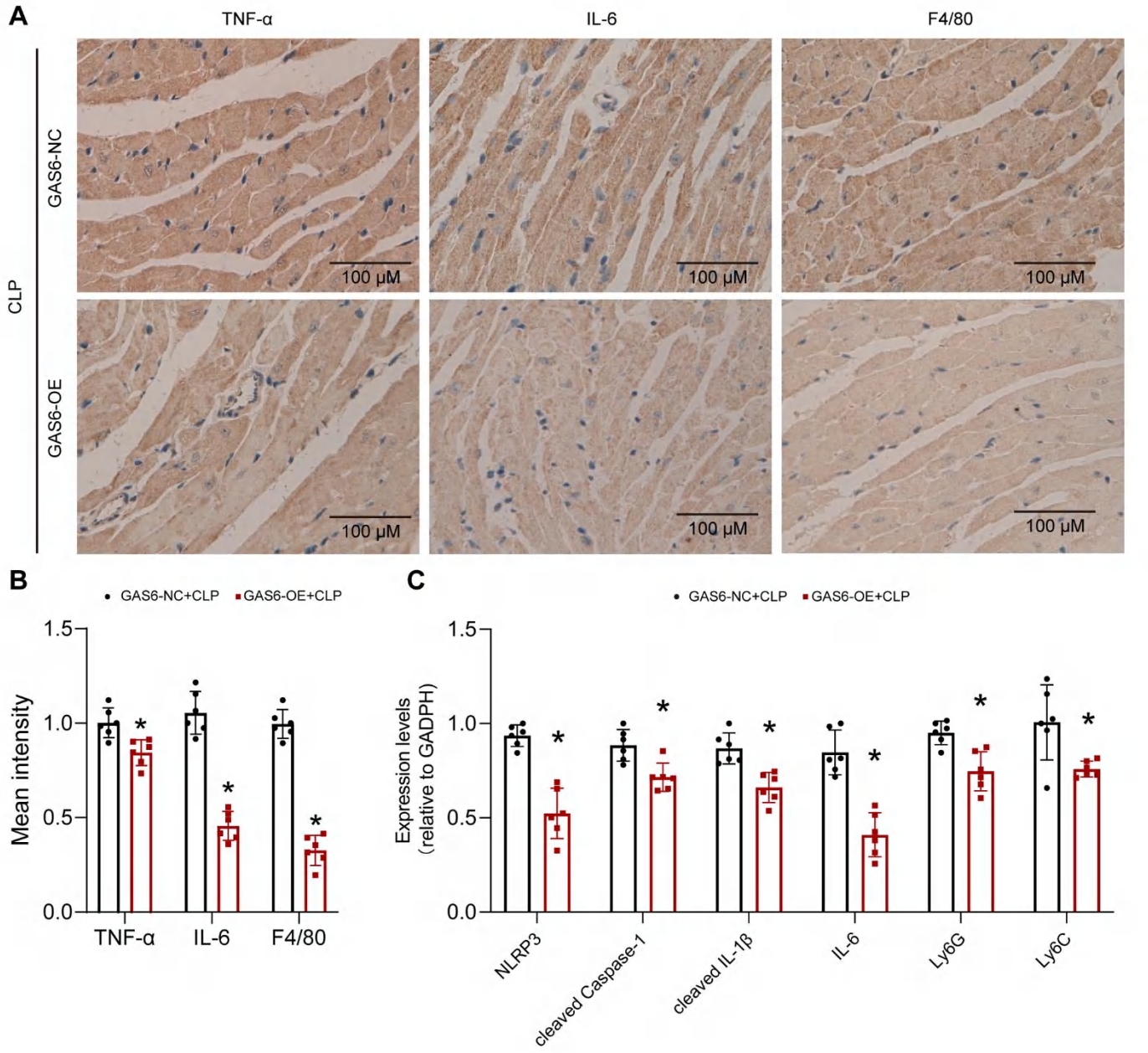
Supplementary Figure 12



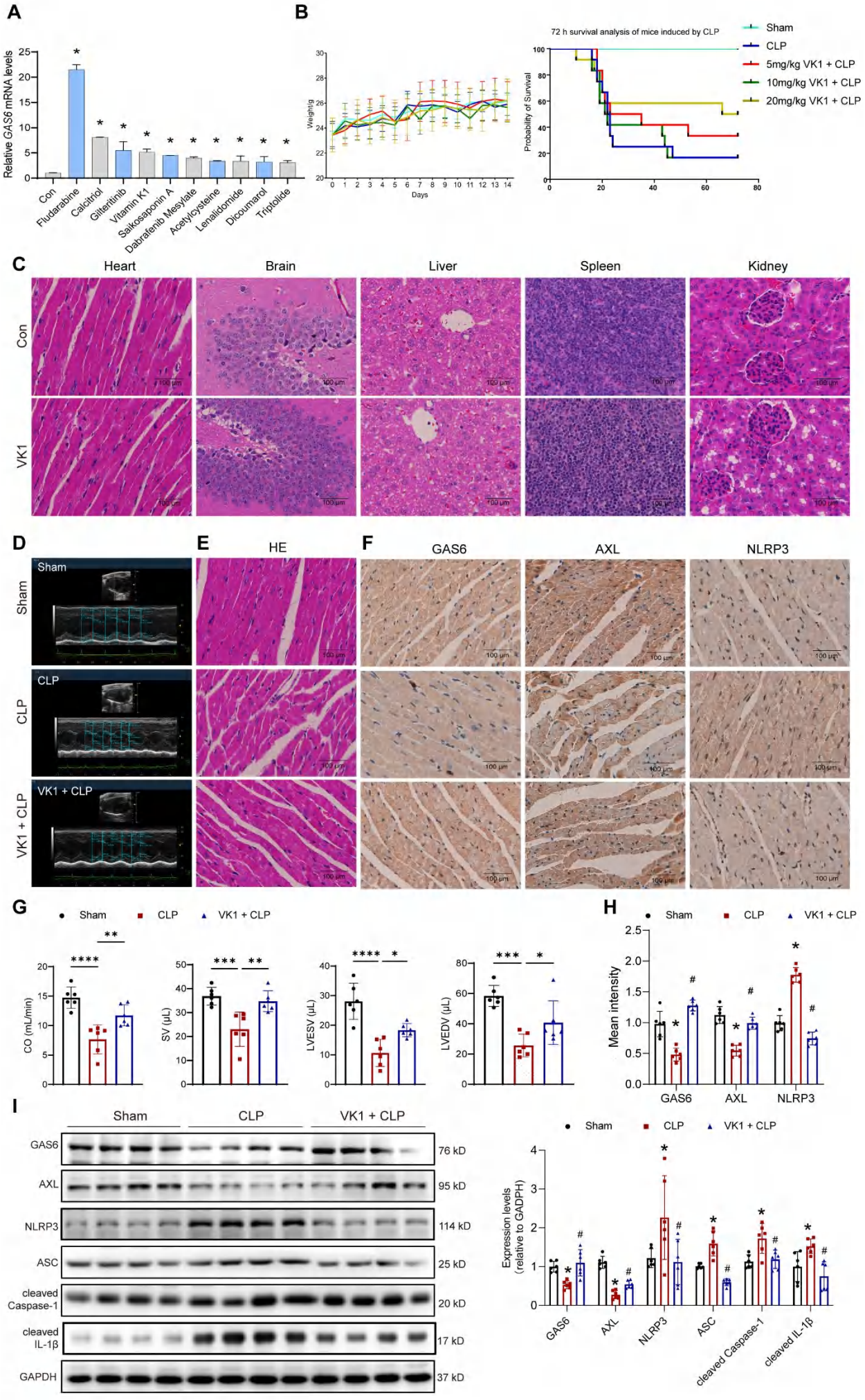
Supplementary Figure 6



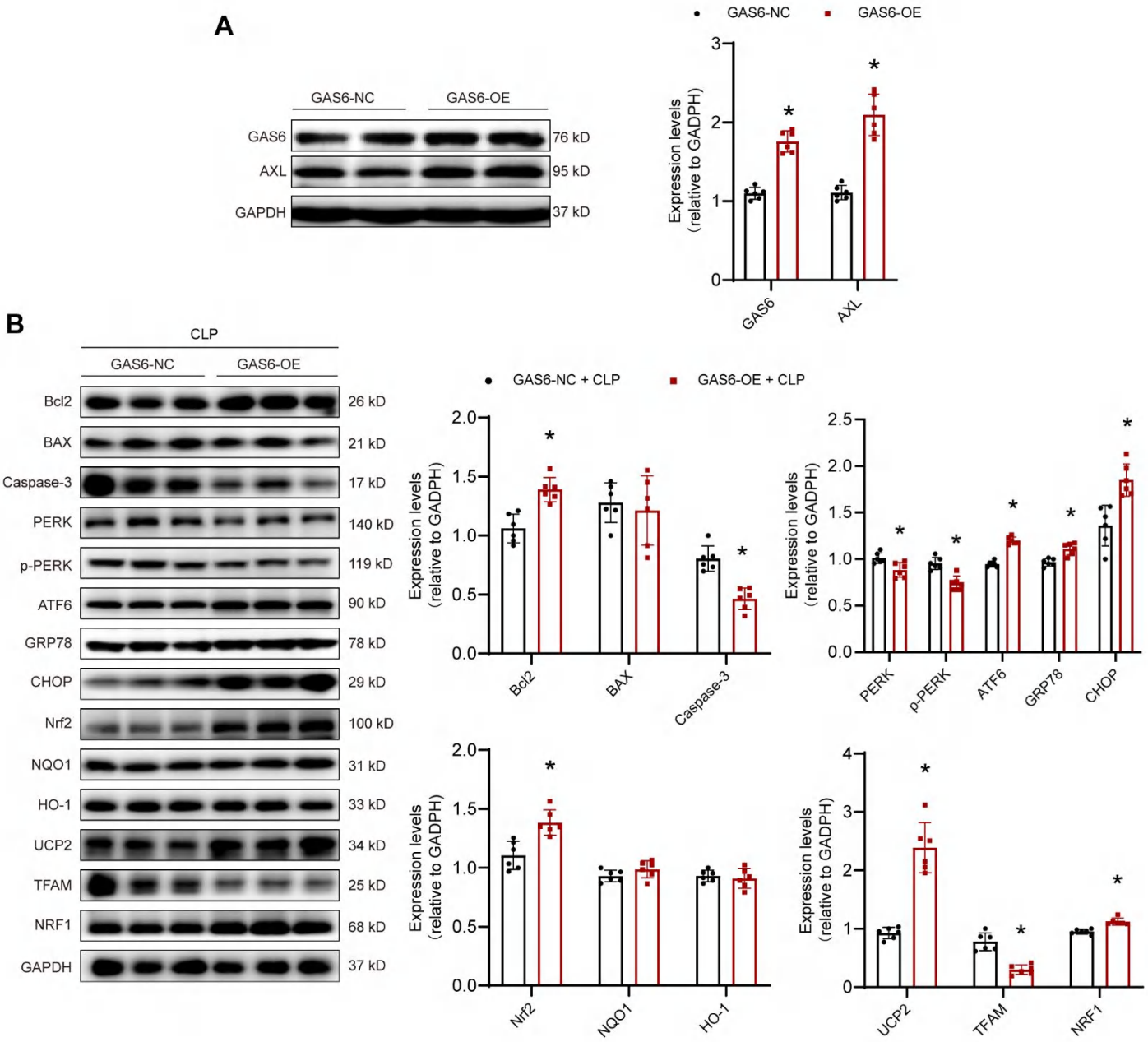
Supplementary Figure 13



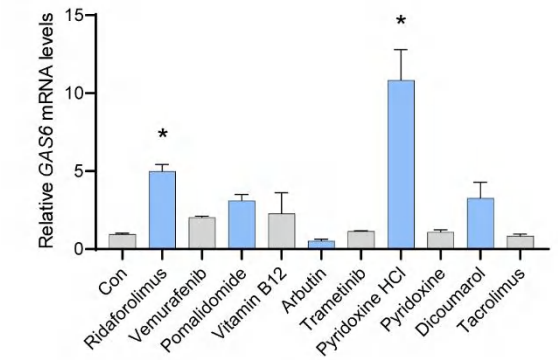
Supplementary Figure 7

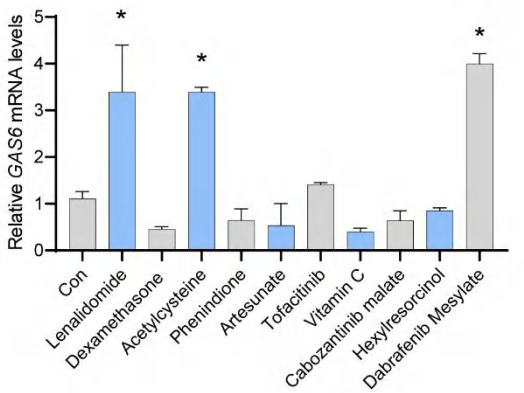


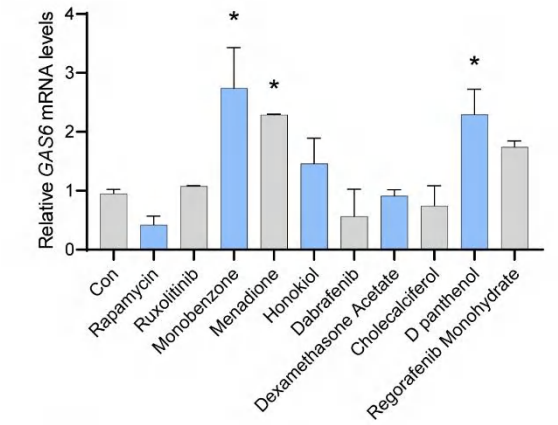
Supplementary Figure 8

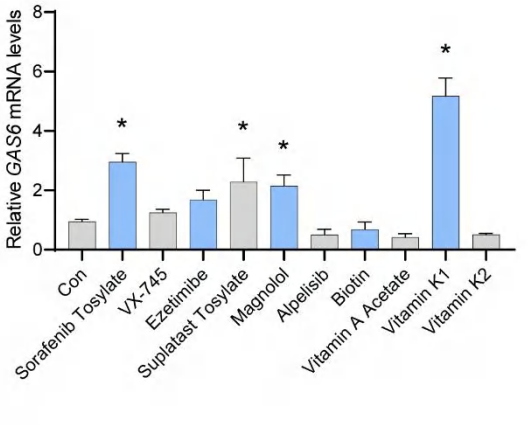


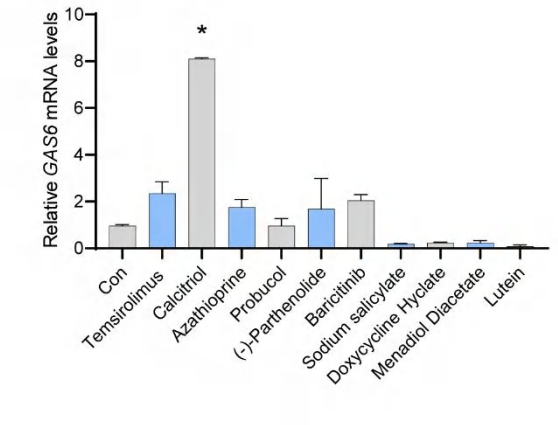
Supplementary Figure 14

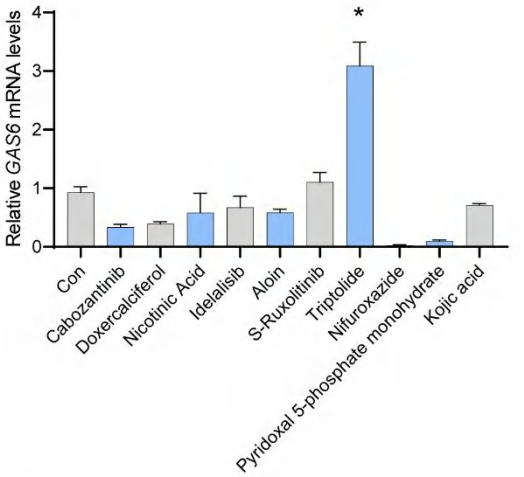


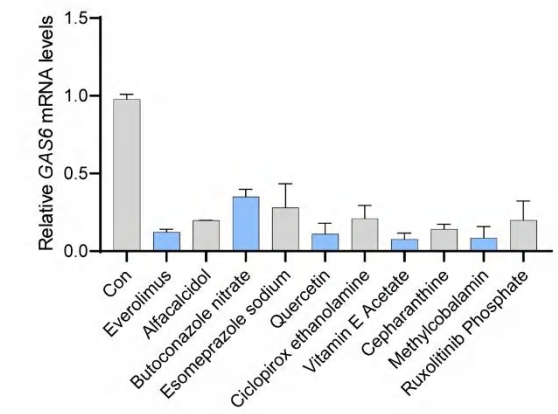


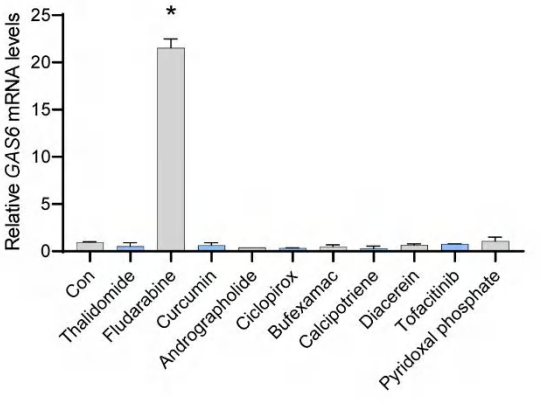




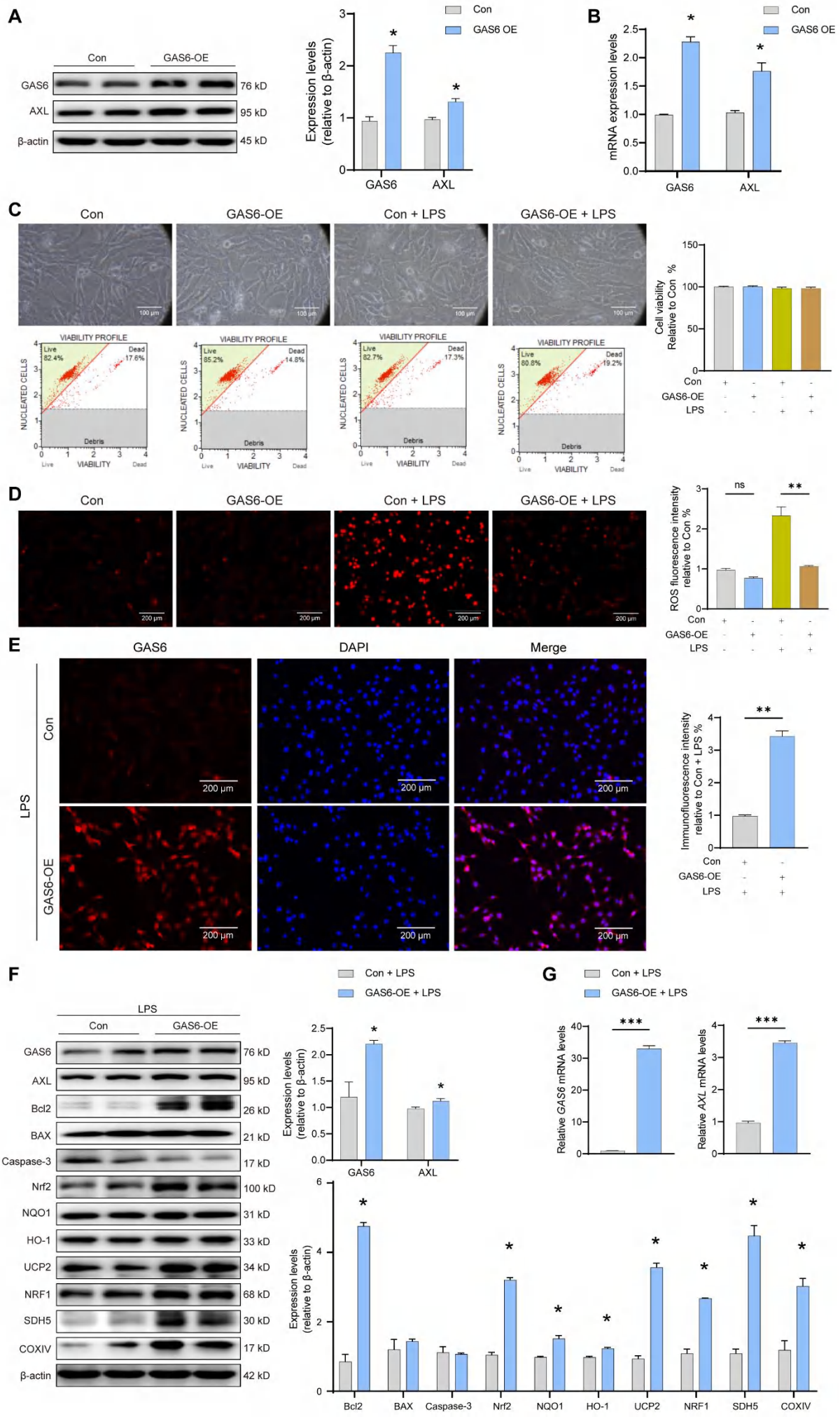




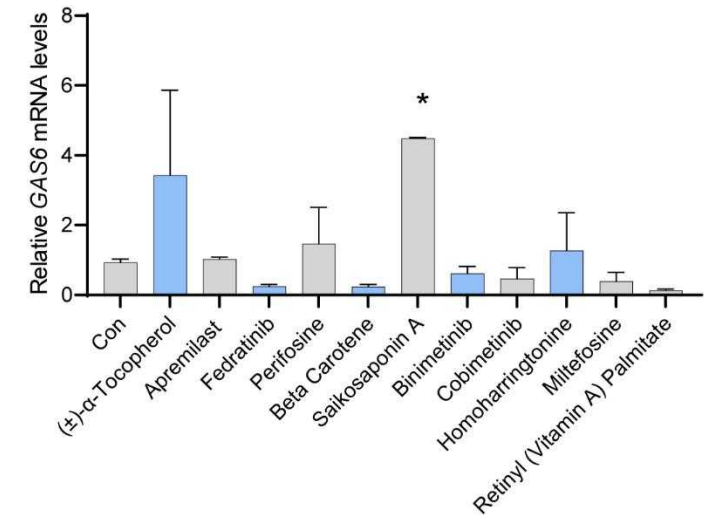


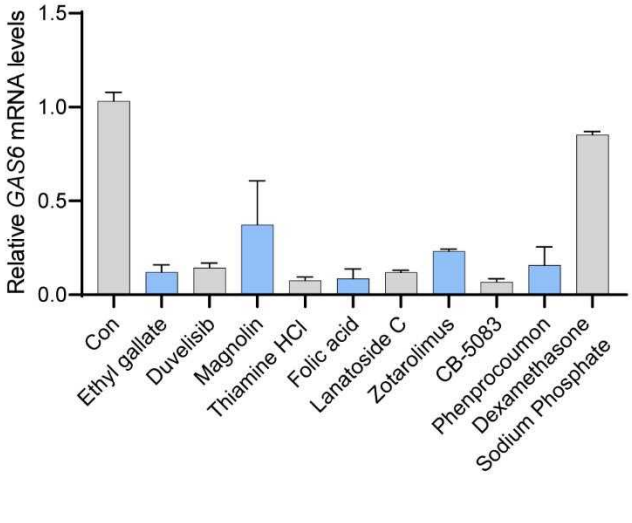


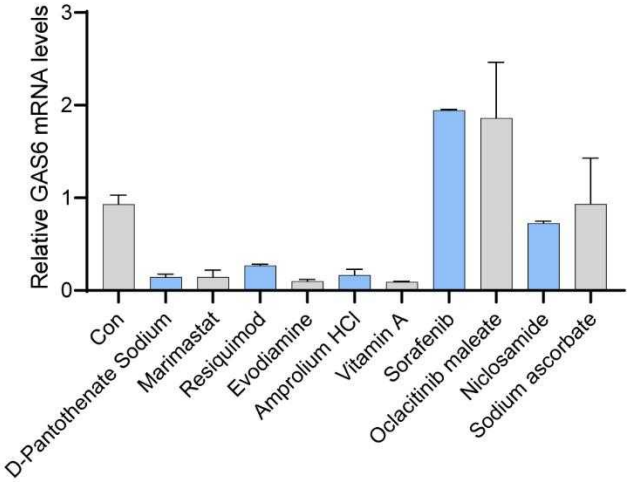
Supplementary Figure 9

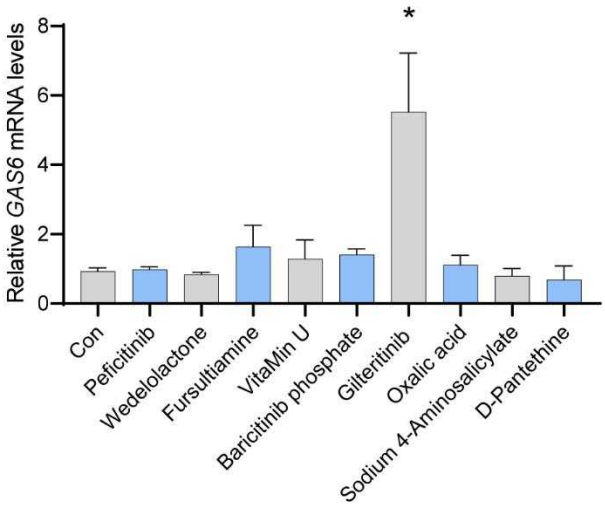


Supplementary Figure 15

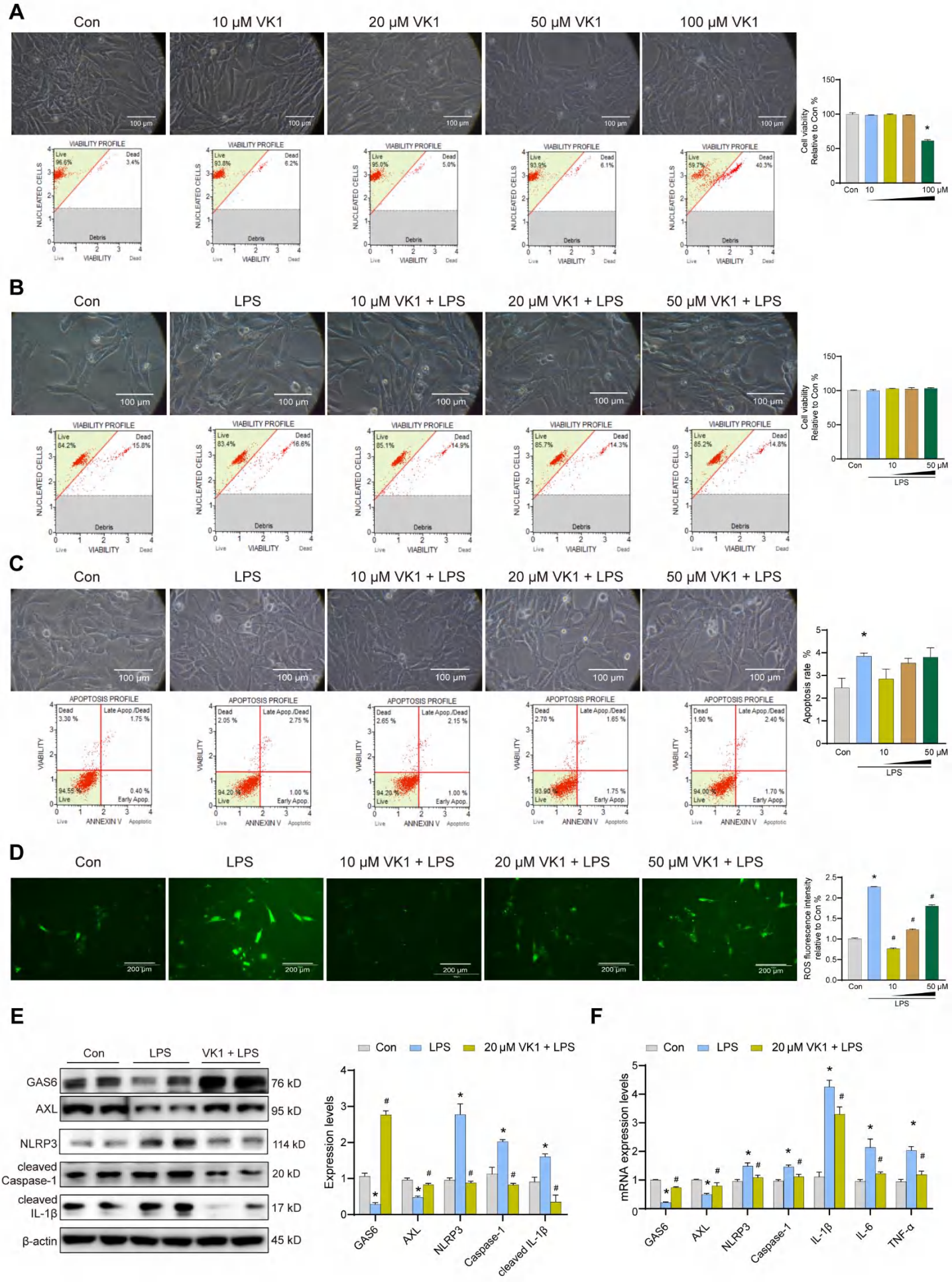




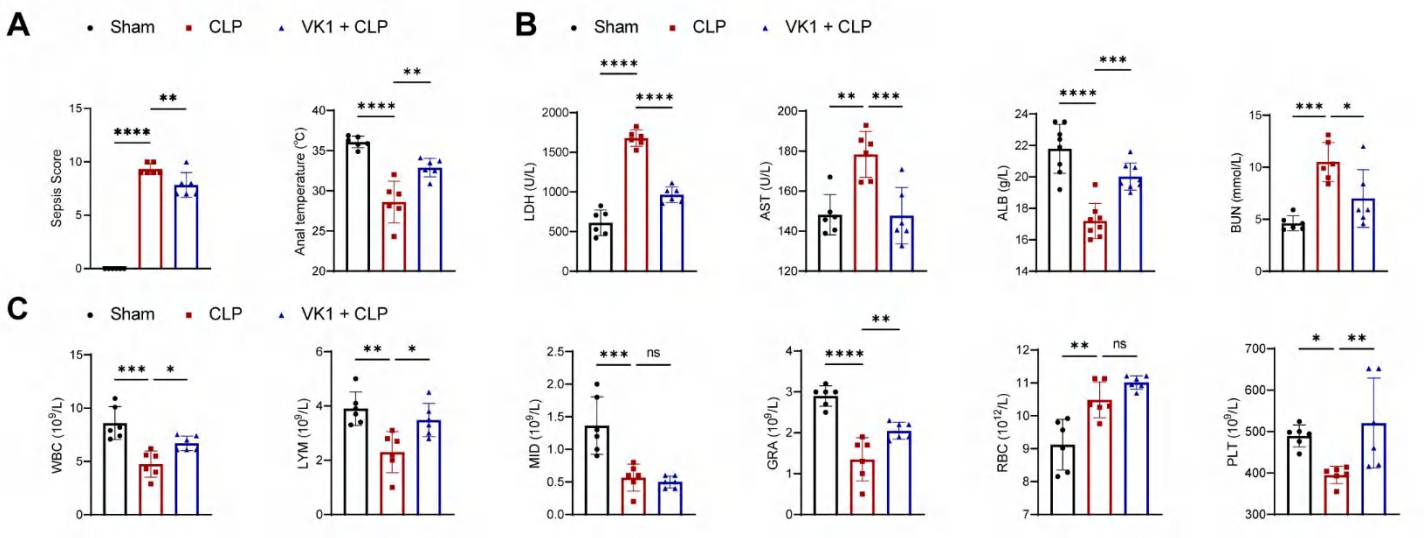




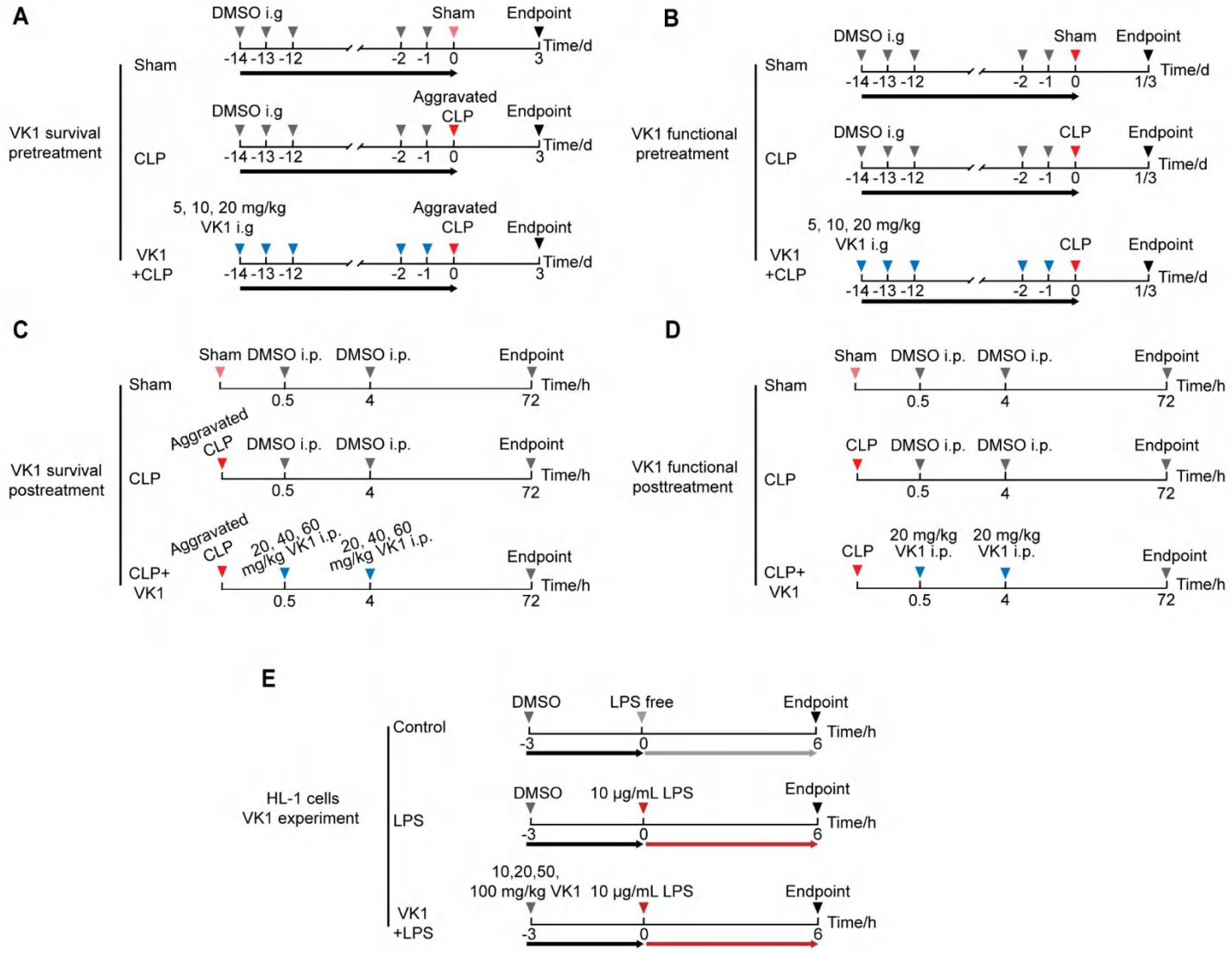
Supplementary Figure 16



Supplementary Figure 17



Supplementary Figure 18



SUPPLEMENTAL Materials

SUPPLEMENTAL TABLES

Table S1 Baseline characteristics of patients with sepsis and non-sepsis.

Variables	Total(n=40)	Non-Sepsis (n=20)	Sepsis (n=20)	P value
Age (years)	55.18±15.52	57.10±14.02	53.25±16.66	0.4456
Male gender (%)	26(65.00%)	14(70.00%)	12(60.00%)	0.5070
BMI	24.8125±3.76	23.77±3.97	25.86±3.43	0.2220
SOFA	——	——	12.35±3.26	——
Renal dysfunction	7(17.50%)	3(15.00%)	4(20.00%)	0.9990
Respiratory dysfunction	7(17.50%)	1(5.00%)	6(30.00%)	0.0960
Liver dysfunction	13(32.500%)	4(20.00%)	9(45.00%)	0.0910
Heart dysfunction	9(22.50%)	2(10.00%)	7(35.00%)	0.1130
Diabetes mellitus	9(22.50%)	4(20.00%)	5(25.00%)	0.9990
Fatty liver	5(12.50%)	3(15.00%)	2(10.00%)	0.9990
ALT	35.92±38.15	26.80±20.58	45.05±48.17	0.1371
AST	46.70±56.48	25.9±14.14	67.50±72.90	0.0194
GGT	50.90±66.76	27.9±15.35	73.90±87.29	0.0295
ALP	116.78±107.25	84.4±26.82	149.15±142.09	0.0584
RBC	3.88±1.70	4.93±1.83	2.87±0.58	<0.0001
HGB	109.14±30.89	133.22±22.13	86.26±17.92	<0.0001
WBC	9.99±6.04	7.33±3.46	12.52±6.82	0.0063
PLT	174.00±80.24	208.21±60.95	141.50±82.82	0.0085

Data are expressed as mean ± SEM, median, or percent.

BMI: Body mass index; ALT: glutamic-pyruvic transaminase; AST: glutamic oxalacetic transaminase; GGT: glutamyl transpeptidase; ALP: alkaline phosphatase; RBC: red blood cell; HGB: hemoglobin; WBC: white blood cell; PLT: blood platelet.

Table S2 Baseline characteristics of patients with heart failure and non-heart failure.

Variables	Total(n=20)	Non-Heart failure (n=10)	Heart failure (n=10)	*P* value
Age (years)	54.15±15.20	50.8±19.71	57.50±7.16	0.3505
Male gender (%)	14(70.00%)	6(60.00%)	8(80.00%)	0.3290
BMI	23.45±4.22	22.84±3.58	24.06±4.70	0.5433
Smoking	9(45.00%)	4(40.00%)	5(50.00%)	0.6530
Alcohol consumption	11(55.00%)	5(50.00%)	6(60.00%)	0.6530
Medication history	9(45.00%)	5(50.00%)	4(40.00%)	0.6530
SBP	120.95±17.30	120.70±21.18	121.20±12.24	0.9518
DBP	72.40±10.46	71.50±11.10	73.30±9.69	0.7182
NYHA Class	2.70±0.78	2.20±0.75	3.20±0.40	0.0024
Heart rate	83.95±11.99	85.70±15.94	82.20±5.25	0.5393
HFrEF	4(40.00%)	0(0)	4(40.00%)	0.0870
LVEF	57.45±12.58	63.70±6.25	51.20±14.13	0.0259
LVIDd	9..68±2.01	10.15±2.43	9.21±1.32	0.3211
RVIDd	17.05±2.62	15.60±0.92	18.50±2.94	0.0112
LVEDd	48.80±9.48	43.30±4.17	54.30±10.10	0.0074
NT-proBNP	914.94±809.90	241.88±84.24	1475.00±685.03	<0.0001
Albumin	38.43±4.88	39.21±4.92	37.65±4.72	0.5010
Sodium	139.20±3.28	140.30±3.38	138.10±2.77	0.1484
Inosinic acid	68.25±17.87	65.40±19.61	71.10±15.42	0.5018
Hemoglobin	118.74±34.42	113.38±42.38	124.10±22.72	0.5121
CHD	10(50.00%)	4(40.00%)	6(60.00%)	0.1780
Hypertension	8(40.00%)	4(40.00%)	4(40.00%)	1.0000
Pulmonary hypertension	2(10.00%)	0(0)	2(20.00%)	0.1360
Heart failure duration (d)	194.75±488.83	0.00±0.00	389.50±634.08	0.0819
PCI	3(30.00%)	0(0)	3(30.00%)	0.0600

Data are expressed as mean ± SEM, median, or percent.

BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; NYHA Class, The New York Heart Association functional classification; LVEF: Left ventricular ejection fraction; LVIDd: left ventricular internal dimension diastole; RVIDd: right ventricular internal dimension, diastole; LVEDd: left ventricular end diastolic diameter; CHD: Coronary artery disease; NT-proBNP, N-terminal pro-B type natriuretic peptide; PCI: percutaneous coronary intervention.

Variables	Score and description
Appearance	0- Coat is smooth
	1- Patches of hair piloerected
	2- Majority of back is piloerected
	3- Piloerection may or may not be present, mouse appears “puffy”
	4- Piloerection may or may not be present, mouse appears emaciated
Level of consciousness	0- Mouse is active
	1- Mouse is active but avoids standing upright
	2- Mouse activity is noticeably slowed. The mouse is still ambulant.
	3- Activity is impaired. Mouse only moves when provoked, movements have a tremor
	4- Activity severely impaired. Mouse remains stationary when provoked, with possible tremor
Activity	0- Normal amount of activity. Mouse is any of: eating, drinking, climbing, running, fighting
	1- Slightly suppressed activity. Mouse is moving around bottom of cage
	2- Suppressed activity. Mouse is stationary with occasional investigative movements
	3- No activity. Mouse is stationary
	4- No activity. Mouse experiencing tremors, particularly in the hind legs
Response to stimulus	0- Mouse responds immediately to auditory stimulus or touch
	1- Slow or no response to auditory stimulus; strong response to touch (moves to escape)
	2- No response to auditory stimulus; moderate response to touch (moves a few steps)
	3- No response to auditory stimulus; mild response to touch (no locomotion)
	4- No response to auditory stimulus. Little or no response to touch. Cannot right itself if pushed over
Eyes	0- Open
	1- Eyes not fully open, possibly with secretions
	2- Eyes at least half closed, possibly with secretions
	3- Eyes half closed or more, possibly with secretions
	4- Eyes closed or milky
Respiration rate	0- Normal, rapid mouse respiration
	1- Slightly decreased respiration (rate not quantifiable by eye)
	2- Moderately reduced respiration (rate at the upper range of quantifying by eye)
	3- Severely reduced respiration (rate easily countable by eye, 0.5 s between breaths)
	4- Extremely reduced respiration (>1 s between breaths)
Respiration quality	0- Normal
	1- Brief periods of laboured breathing
	2- Laboured, no gasping
	3- Laboured with intermittent gasps
	4- Gasping

Table S3 Murine sepsis score (MSS)

Table S4 Information about correlation immunohistochemical antibody

Antibodies	Concentration	Product No	Manufacturers
anti-GAS6	1:200	bs-7549R	Bioss Biotechnology Co., Ltd, Beijing, China
anti-AXL	1:200	bs-5180R	Bioss Biotechnology Co., Ltd, Beijing, China
anti-NLRP3	1:200	bs-10021R	Bioss Biotechnology Co., Ltd, Beijing, China
anti-IL-6	1:200	GB11117	Servicebio, Wuhan, Hubei, China
anti-MPO	1:200	22225-1-AP	Proteintech, Wuhan, China
anti-F4/80	1:200	GB11027	Servicebio, Wuhan, Hubei, China
anti-Ly6G	1:200	GB11229	Servicebio, Wuhan, Hubei, China
anti-TNF-α	1:200	GB11188	Servicebio, Wuhan, Hubei, China

Table S5 Information about correlation primers

Primer	Sequences
mouse-GAS6	F：5 ‘-TACCTACAGGCTCAACTACACC-3’
	R：5 ‘-CTCAACTGCCAGGACCAC-3’
mouse-AXL	F：5 ‘-ATGGCCGACATTGCCAGTG-3’
	R：5 ‘-CGGTAGTAATCCCCGTTGTAGA-3’
mouse-NLRP3	F：5 ‘-ACCTCAACAGTCGCTACAC-3’
	R：5 ‘-GTCCTCGGGCTCAAACA-3’
mouse-Caspase-1	F：5 ‘-AGAACAGAACAAAGAAGATGGCACA-3’
	R：5 ‘-GTGCCATCTTCTTTGTTCTGTTCTT-3’
mouse-IL-1β	F：5 ‘-TGGACCTTCCAGGATGAGGACA-3’
	R：5 ‘-GTTCATCTCGGAGCCTGTAGTG-3’
mouse-IL-6	F：5 ‘-TACCACTTCACAAGTCGGAGGC-3’
	R：5 ‘-CTGCAAGTGCATCATCGTTGTT-3’
mouse-TNF-α	F：5 ‘-GGTGCCTATGTCTCAGCCTCTT-3’
	R：5 ‘-GCCATAGAACTGATGAGAGGGAG-3’
mouse-β-actin	F：5 ‘-CTTTTCCAGCCTTCCTTCTT-3’
	R：5 ‘-GGTCTTTACGGATGTCAACG-3’
rat-GAS6	F：5 ‘-AAACGGTCAAGGCCAATACA -3’
	R：5 ‘-ATGCGAGCCACGACTTCTAC-3’
rat-AXL	F：5 ‘-ATCGGAGGAAGAAGGAGACG-3’
	R：5 ‘-TGCCCAGACTGTTCAAGGTG-3’
rat-NLRP3	F：5 ‘-CAGAAGCTGGGGTTGGTGAA-3’
	R：5 ‘-CCCATGTCTCCAAGGGCATT-3’
rat-Caspase-1	F：5 ‘-CTGGAGCTTCAGTCAGGTCC-3’
	R：5 ‘-CTTGAGGGAACCACTCGGTC-3’
rat-IL-1β	F：5 ‘-AACTGTGAAATAGCAGCTTTCG-3’
	R：5 ‘-CTGTGAGATTTGAAGCTGGATG-3’
rat-IL-6	F：5 ‘-TCCGGAGAGGAGACTTCACA-3’
	R：5 ‘-TGCCATTGCACAACTCTTTTCT-3’
rat-TNF-α	F：5 ‘-ACTGAACTTCGGGGTGATCG-3’
	R：5 ‘-TGGTGGTTTGCTACGACGTG-3’
rat-β-actin	F：5 ‘-AGAGCTATGAGCTGCCTGAC -3’
	R：5 ‘-AATTGAATGTAGTTTCATGGATG-3’

Table S6 Information about antibodies used in Western blot

Antibodies	Concentration	Product No	Manufacturers
anti-GAS6	1:1000	bs-7549R	Bioss Biotechnology Co., Ltd, Beijing, China
anti-AXL	1:1000	bs-5180R	Bioss Biotechnology Co., Ltd, Beijing, China
anti-NLRP3	1:1000	bs-10021R	Bioss Biotechnology Co., Ltd, Beijing, China
anti-Caspase-1	1:1000	GB11383	Servicebio, Wuhan, Hubei, China
anti-IL-1	1:1000	bs-0812R	Bioss Biotechnology Co., Ltd, Beijing, China
anti-ASC	1:500	sc-514414	Santa Cruz Biotechnology, Dallas, TX, USA
anti-IL-6	1:500	sc-57315	Santa Cruz Biotechnology, Dallas, TX, USA
anti-Ly6G	1:1000	bs-2576R	Bioss Biotechnology Co., Ltd, Beijing, China
anti-Ly6C	1:1000	A33313	Boster Biological Technology Co., Ltd, Wuhan, Hubei, China
anti-BAX	1:1000	2772s	Cell Signaling Technology, Inc, Danvers, Massachusetts, USA
anti-Bcl2	1:1000	BA0412	Boster Biological Technology Co., Ltd, Wuhan, Hubei, China
anti-Caspase-3	1:500	sc-56053	Santa Cruz Biotechnology, Dallas, TX, USA
anti-Nrf2	1:1000	PB9290	Boster Biological Technology Co., Ltd, Wuhan, Hubei, China
anti-HO-1	1:1000	ab189491	Abcam Biotechnology, Cambridge, United Kingdom
anti-NQO1	1:500	sc-393736	Santa Cruz Biotechnology, Dallas, TX, USA
anti-ATF6	1:500	sc-166659	Santa Cruz Biotechnology, Dallas, TX, USA
anti-GRP78	1:1000	3177s	Cell Signaling Technology, Inc, Danvers, Massachusetts, USA
anti-p-PERK	1:1000	bs-23340R	Bioss Biotechnology Co., Ltd, Beijing, China
anti-PERK	1:1000	3192s	Cell Signaling Technology, Inc, Danvers, Massachusetts, USA
anti-CHOP	1:1000	A00311-2	Boster Biological Technology Co., Ltd, Wuhan, Hubei, China
anti-NRF1	1:500	sc-101102	Santa Cruz Biotechnology, Dallas, TX, USA
anti-UCP2	1:1000	GB11377	Servicebio, Wuhan, Hubei, China
anti-TFAM	1:500	sc-166965	Santa Cruz Biotechnology, Dallas, TX, USA
anti-GAPDH	1:1000	GB11002	Servicebio, Wuhan, Hubei, China
anti-β-actin	1:1000	GB11001	Servicebio Technology Co., Ltd, Wuhan, China
Goat anti-mouse IgG	1:5000	7076s	Cell Signaling Technology, Inc., Danvers, Massachusetts, USA
Goat anti-rabbit IgG	1:5000	BA1054	Boster Biological Technology Co., Ltd., CA, USA

Table S7 Information about FDA-approved drugs library used in this study

No	Barcode	Catalog Number	Product Name	CAS Number	M.w.	Significant Toxicity (10 μM)
1A1	54416774	S1022	Ridaforolimus (Deforolimus, MK-8669)	572924-54-0	990.21	NO
1B1	46002394	S1029	Lenalidomide (CC-5013)	191732-72-6	259.26	NO
1C1	55195245	S1039	Rapamycin (Sirolimus)	53123-88-9	914.18	NO
1D1	55191625	S1040	Sorafenib Tosylate	475207-59-1	637.03	NO
1E1	55449921	S1044	Temsirolimus (CCI-779, NSC 683864)	162635-04-3	1030.29	NO
1F1	54412381	S1119	Cabozantinib (XL184, BMS-907351)	849217-68-1	501.51	NO
1G1	55210717	S1120	Everolimus (RAD001)	159351-69-6	958.22	NO
1H1	45997586	S1193	Thalidomide	50-35-1	258.23	NO
1A2	54527905	S1267	Vemurafenib (PLX4032, RG7204)	918504-65-1	489.92	NO
1B2	55420235	S1322	Dexamethasone (DHAP)	50-02-2	392.46	NO
1C2	45917691	S1378	Ruxolitinib (INCB018424)	941678-49-5	306.37	NO
1D2	54408717	S1458	VX-745	209410-46-8	436.26	NO
1E2	55206536	S1466	Calcitriol	32222-06-3	416.64	NO
1F2	55199021	S1467	Doxercalciferol	54573-75-0	412.65	NO
1G2	55193428	S1468	Alfacalcidol	41294-56-8	400.64	NO
1H2	54469915	S1491	Fludarabine	21679-14-1	285.23	NO
1A3	45529212	S1567	Pomalidomide	19171-19-8	273.24	NO
1B3	55203466	S1623	Acetylcysteine	616-91-1	163.19	NO
1C3	54491197	S1652	Monobenzone	103-16-2	200.23	NO
1D3	45529577	S1655	Ezetimibe	163222-33-1	409.40	NO
1E3	46102129	S1721	Azathioprine	446-86-6	277.26	NO
1F3	54363749	S1744	Nicotinic Acid	59-67-6	123.11	NO
1G3	54404701	S1833	Butoconazole nitrate	64872-77-1	474.79	NO
1H3	55471402	S1848	Curcumin	458-37-7	368.38	NO
1A4	46489757	S1902	Vitamin B12	68-19-9	1355.37	NO
1B4	55416552	S1921	Phenindione	83-12-5	222.24	NO
1C4	55578687	S1949	Menadione	58-27-5	172.18	NO
1D4	46484393	S2015	Suplatast Tosylate	94055-76-2	499.64	NO
1E4	54422743	S2119	Probucol	23288-49-5	516.84	NO
1F4	55418076	S2226	Idelalisib (CAL-101, GS-1101)	870281-82-6	415.42	NO
1G4	55199109	S2233	Esomeprazole sodium	161796-78-7	367.40	NO
1H4	46048734	S2261	Andrographolide	5508-58-7	350.45	NO
1A5	55203563	S2263	Arbutin	497-76-7	272.25	NO
1B5	54408494	S2265	Artesunate	88495-63-0	384.42	NO
1C5	55585080	S2310	Honokiol	35354-74-6	266.33	NO
1D5	46084158	S2321	Magnolol	528-43-8	266.33	NO
1E5	55555229	S2341	(-)-Parthenolide	20554-84-1	248.32	NO

1F5	55460561	S2375	Aloin	1415-73-2	418.39	NO
1G5	55460533	S2391	Quercetin	117-39-5	302.24	NO
1H5	54493851	S2528	Ciclopirox	29342-05-0	207.27	NO
1A6	55187768	S2673	Trametinib (GSK1120212)	871700-17-3	615.39	NO
1B6	46050809	S2789	Tofacitinib (CP-690550,Tasocitinib)	477600-75-2	312.37	NO
1C6	46077641	S2807	Dabrafenib (GSK2118436)	1195765-45-7	519.56	NO
1D6	55199049	S2814	Alpelisib (BYL719)	1217486-61-7	441.47	NO
1E6	55209289	S2851	Baricitinib (LY3009104, INCB028050)	1187594-09-7	371.42	NO
1F6	55508075	S2902	S-Ruxolitinib (INCB018424)	941685-37-6	306.37	NO
1G6	55472772	S3019	Ciclopirox ethanolamine	41621-49-2	268.35	NO
1H6	54437559	S3023	Bufexamac	2438-72-4	223.27	NO
1A7	46083002	S3113	Pyridoxine HCl	58-56-0	205.64	NO
1B7	45499662	S3114	Vitamin C	50-81-7	176.12	NO
1C7	54469834	S3124	Dexamethasone Acetate	1177-87-3	434.50	NO
1D7	55464316	S3130	Biotin (Vitamin B7)	58-85-5	244.31	NO
1E7	46229537	S3137	Sodium salicylate	54-21-7	161.11	NO
1F7	55475528	S3604	Triptolide (PG490)	38748-32-2	360.40	NO
1G7	55578642	S3681	Vitamin E Acetate	58-95-7	472.74	NO
1H7	55452693	S3739	Calcipotriene	112965-21-6	412.60	NO
1A8	45823293	S3980	Pyridoxine	65-23-6	169.18	NO
1B8	55535567	S4001	Cabozantinib malate (XL184)	1140909-48-3	635.59	NO
1C8	43999908	S4063	Cholecalciferol (Vitamin D3)	67-97-0	384.64	NO
1D8	54425069	S4083	Vitamin A Acetate	127-47-9	328.49	NO
1E8	54530574	S4163	Doxycycline Hyclate	24390-14-5	512.94	NO
1F8	46203086	S4182	Nifuroxazide	965-52-6	275.22	NO
1G8	56053831	S4238	Cepharanthine	481-49-2	606.71	NO
1H8	54410212	S4267	Diacerein	13739-02-1	368.29	NO
1A9	55207745	S4299	Dicoumarol	66-76-2	336.29	NO
1B9	55209901	S4571	Hexylresorcinol	136-77-6	194.27	NO
1C9	54409767	S4695	D panthenol	81-13-0	205.25	NO
1D9	54440374	S4698	Vitamin K1	84-80-0	450.70	NO
1E9	46213671	S4779	Menadiol Diacetate	573-20-6	258.27	NO
1F9	47036060	S4871	Pyridoxal 5-phosphate monohydrate	41468-25-1	265.16	NO
1G9	55521125	S4994	Methylcobalamin	13422-55-4	1344.38	NO
1H9	46248800	S5001	Tofacitinib (CP-690550) Citrate	540737-29-9	504.49	NO
1A10	47463042	S5003	Tacrolimus (FK506)	104987-11-3	804.02	NO
1B10	54430655	S5069	Dabrafenib Mesylate	1195768-06-9	615.67	NO
1C10	55426564	S5077	Regorafenib Monohydrate	1019206-88-2	500.83	NO
1D10	54414606	S5082	Vitamin K2	863-61-6	444.65	NO
1E10	55539164	S5103	Lutein	127-40-2	568.87	NO
1F10	47020953	S5174	Kojic acid	501-30-4	142.11	NO
1G10	55557110	S5243	Ruxolitinib Phosphate	1092939-17-7	404.36	NO
1H10	55556796	S5311	Pyridoxal phosphate	54-47-7	247.14	NO
2A1	54418281	S5454	Saikosaponin D	20874-52-6	780.98	YES

2B1	55546081	S5466	Saikosaponin A	20736-09-8	780.98	NO
2C1	55413994	S5550	Ethyl gallate	831-61-8	198.17	NO
2D1	55537861	S5554	Lanatoside C	17575-22-3	985.12	NO
2E1	55219634	S5558	D-Pantothenate Sodium	867-81-2	241.22	NO
2F1	55545008	S5592	Vitamin A	68-26-8	286.45	NO
2G1	55585094	S5733	Stearic acid	57-11-4	284.48	YES
2H1	54525112	S5754	Baricitinib phosphate	1187595-84-1	469.41	NO
2A2	56024802	S6104	(±)-α-Tocopherol	10191-41-0	430.71	NO
2B2	55424985	S7007	Binimetinib (MEK162, ARRY-162, ARRY-438162)	606143-89-9	441.23	NO
2C2	55416799	S7028	Duvelisib (IPI-145, INK1197)	1201438-56-3	416.86	NO
2D2	55428041	S7091	Zotarolimus(ABT-578)	221877-54-9	966.21	NO
2E2	55557687	S7156	Marimastat (BB-2516)	154039-60-8	331.41	NO
2F2	55436559	S7397	Sorafenib	284461-73-0	464.82	NO
2G2	55537479	S7650	Peficitinib (ASP015K, JNJ-54781532)	944118-01-8	326.39	NO
2H2	55582498	S7754	Gilteritinib (ASP2215)	1254053-43-4	552.71	NO
2A3	55528173	S8034	Apremilast (CC-10004)	608141-41-9	460.50	NO
2B3	54445994	S8041	Cobimetinib (GDC-0973, RG7420)	934660-93-2	531.31	NO
2C3	46458297	S8048	Venetoclax (ABT-199, GDC-0199)	1257044-40-8	868.44	YES
2D3	43855361	S8101	CB-5083	1542705-92-9	413.47	NO
2E3	43999406	S8133	Resiquimod	144875-48-9	314.38	NO
2F3	55577587	S8195	Oclacitinib maleate	1640292-55-2	453.51	NO
2G3	55567312	S9042	Wedelolactone	524-12-9	314.25	NO
2H3	55575179	S9354	Oxalic acid	144-62-7	90.03	NO
2A4	55511276	S2736	Fedratinib (SAR302503, TG101348)	936091-26-8	524.68	NO
2B4	56055641	S9015	Homoharringtonine	26833-87-4	545.62	NO
2C4	55224606	S9102	Magnolin	31008-18-1	416.46	NO
2D4	56015413	S2188	Phenprocoumon	435-97-2,53621-47-9 (sodium salt)	280.32	NO
2E4	55473308	S2382	Evodiamine	518-17-2	303.36	NO
2F4	55466628	S3030	Niclosamide	50-65-7	327.12	NO
2G4	54400147	S6614	Fursultiamine	804-30-8	398.54	NO
2H4	46096943	S4073	Sodium 4-Aminosalicylate	6018-19-5	211.15	NO
2A5	55212494	S1037	Perifosine (KRX-0401)	157716-52-4	461.66	NO
2B5	55548727	S3056	Miltefosine	58066-85-6	407.57	NO
2C5	49534014	S3211	Thiamine HCl (Vitamin B1)	67-03-8	337.27	NO
2D5	55458282	S4028	Dexamethasone Sodium Phosphate	55203-24-2	516.40	NO
2E5	55513375	S4144	Amprolium HCl	137-88-2	315.24	NO
2F5	55508459	S4245	Sodium ascorbate	134-03-2	201.13	NO
2G5	55543552	S4811	VitaMin U	3493-12-7	199.70	NO
2H5	45486111	S5220	D-Pantethine	16816-67-4	554.72	NO
2A6	55467066	S1767	Beta Carotene	7235-40-7	536.87	NO
2B6	54433849	S4126	Retinyl (Vitamin A) Palmitate	79-81-2	524.86	NO
2C6	55214202	S4605	Folic acid	59-30-3	441.40	NO

SUPPLEMENTAL FIGURES

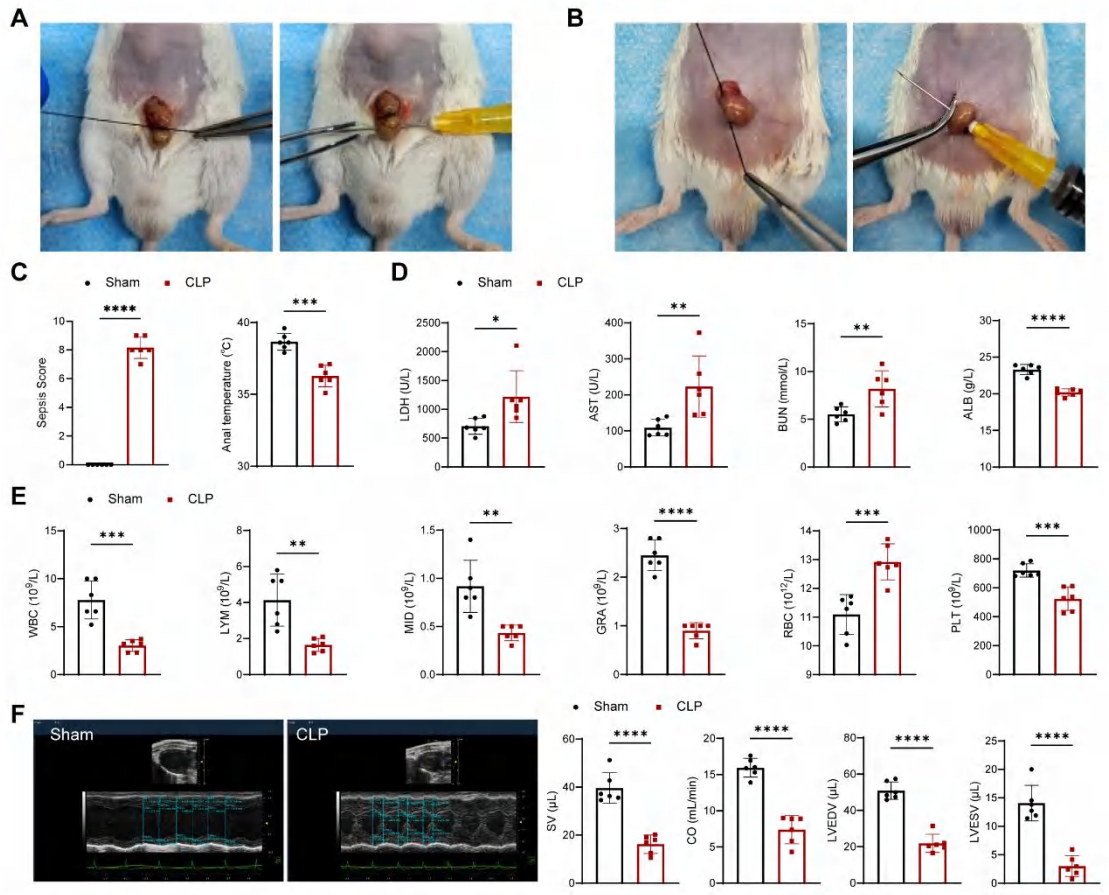


Fig. S1 The construction of sepsis models *in vivo*. (A) Construction of CLP model for functional experiments (left: cecal ligation; right: cecal perforation); **(B)** Construction of aggravated CLP model for survival analysis (left: cecal ligation; right: cecal perforation); **(C)** The sepsis score and anal temperature in mice 8 h following CLP; **(D)** Blood biochemical parameters in mice 8 h following CLP; **(E)** Blood routine parameters in mice 8 h following CLP; **(F)** Representative and quantified (CO, SV, LVEDV and LVESV) echocardiographic results of the long axis in mice 8 h following CLP. n=6 per group, Mean ± SD. $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$ vs. Sham.

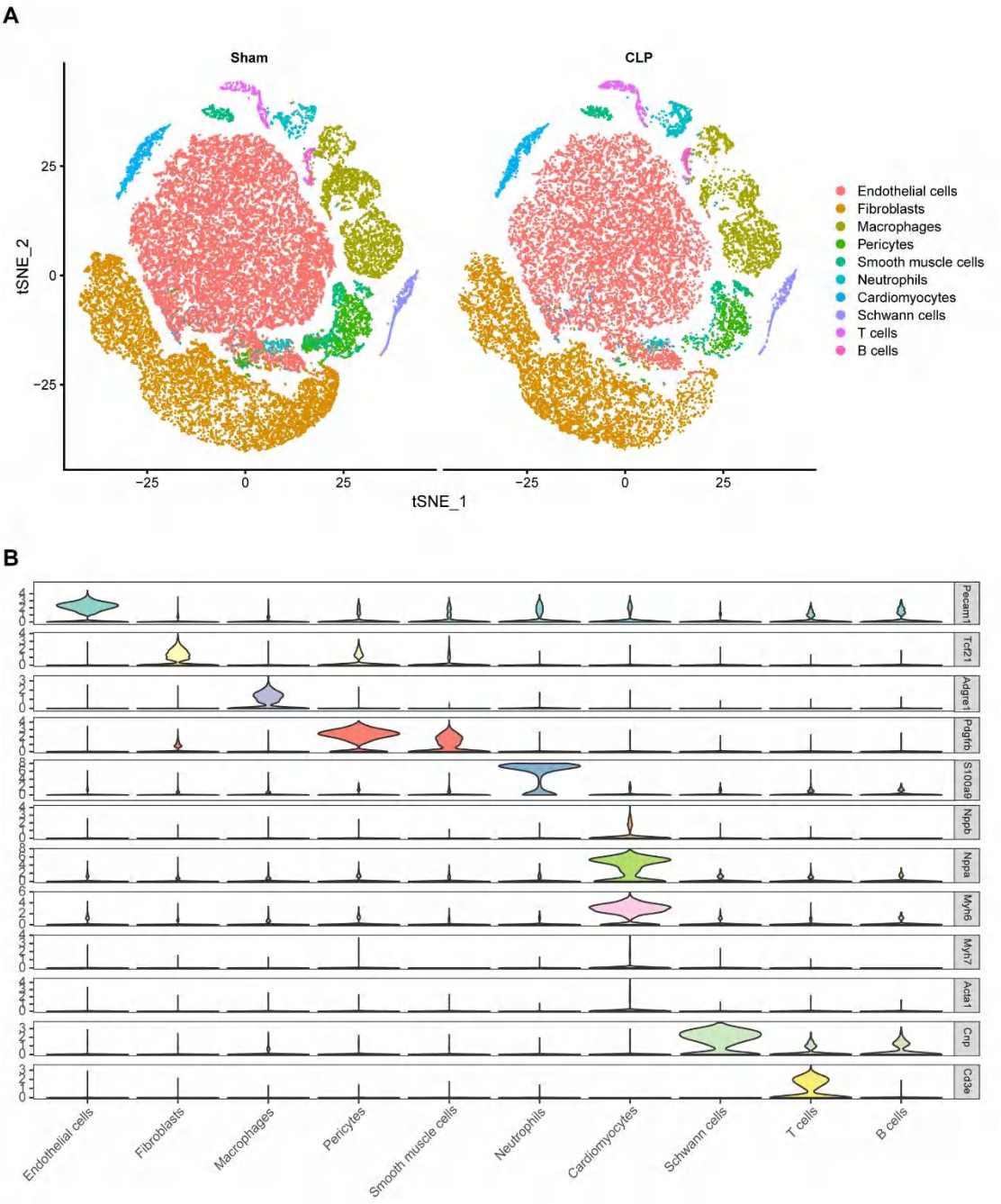


Fig. S2 Supplemental data of Single-cell RNA sequencing in cell clusters of heart tissues. (A) t-distributed Stochastic Neighbor Embedding (t-SNE) visualization of nuclei from hearts of 3 Sham mice and 3 CLP mice. Cells are color-coded according to their different types; **(B)** Violin plots showing single-cell normalized expression of the most discriminative surface markers in the 10 cell populations.

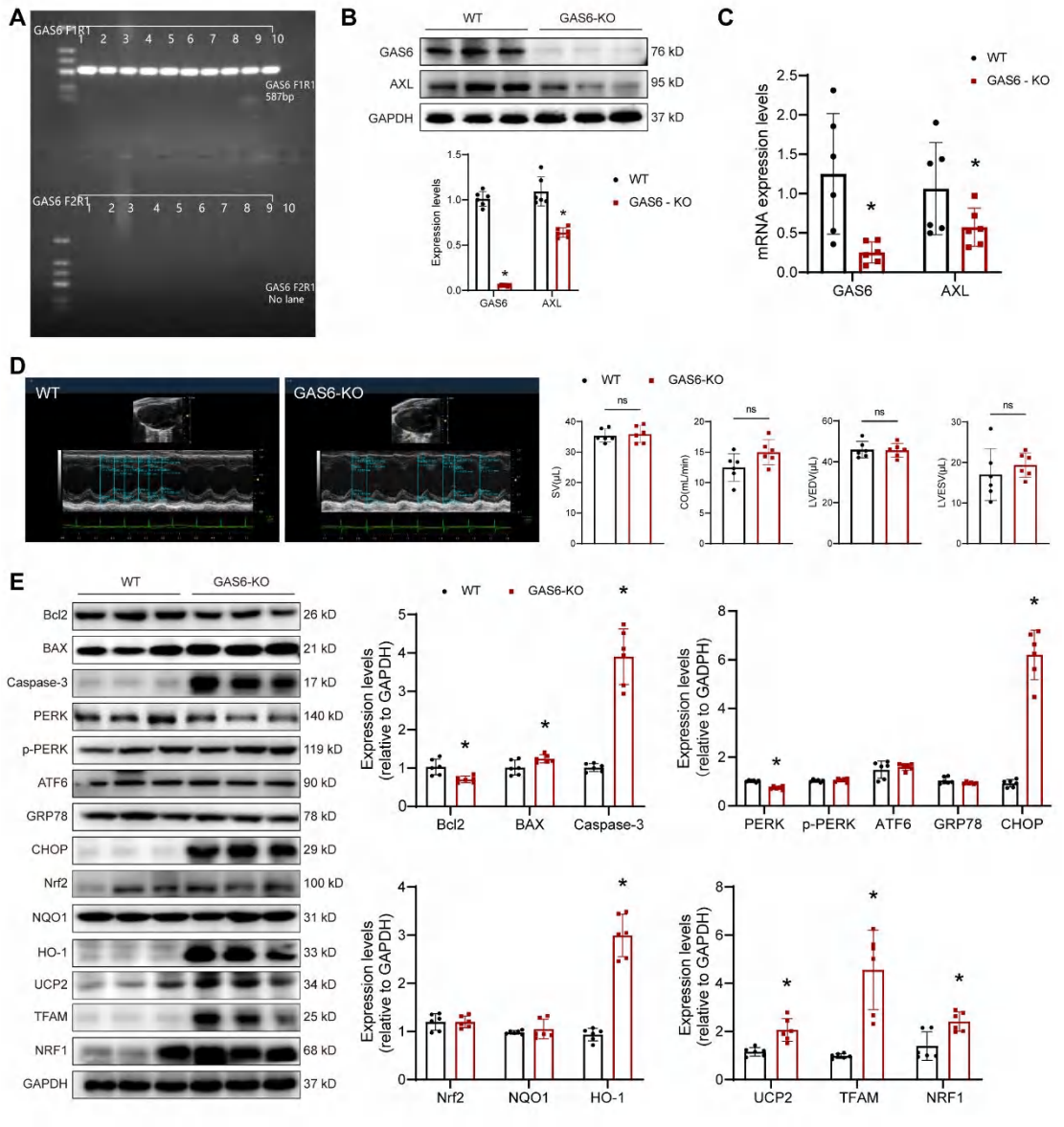


Fig. S3 The effects of GAS6 deficiency alone *in vivo* on CLP-free mice. (A) Southern blot images in mice with GAS6 deficiency, n=10; **(B)** Representative and pooled Western blot analysis of myocardial GAS6 and AXL in mice with GAS6 deficiency. n=6; **(C)** qRT-PCR analysis of myocardial *GAS6* and *AXL* in mice with GAS6 deficiency, n=6; **(D)** Representative and quantified (CO, SV, LVEDV and LVESV) echocardiographic results of the long axis in mice with GAS6 deficiency, n=6; and **(E)** Representative and pooled Western blot analysis of myocardial Bcl2, BAX, Caspase-3, PERK, p-PERK, ATF6, GRP78, CHOP, Nrf2, NQO1, HO-1, UCP2, TFAM and NRF1 in mice with GAS6 deficiency, n=6. Mean ± SD, $^{*}P<0.05$ vs. WT.

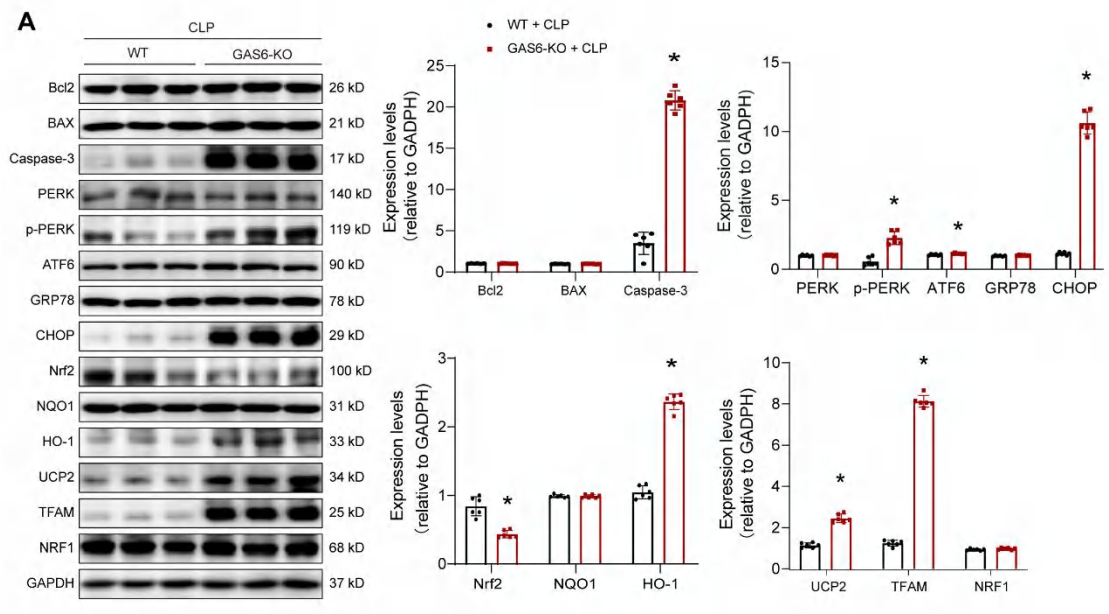


Fig. S4 The effects of GAS6 knockout *in vivo* on CLP-induced various pathways. (A) Representative and pooled Western blot analysis of myocardial Bcl2, BAX, Caspase-3, PERK, p-PERK, ATF6, GRP78, CHOP, Nrf2, NQO1, HO-1, UCP2, TFAM and NRF1 in CLP-injured mice with GAS6-KO. Mean ± SD. n=6 per group, $^{*}P<0.05$. $^{**}P<0.01$, $^{***}P<0.001$, vs. WT-CLP.

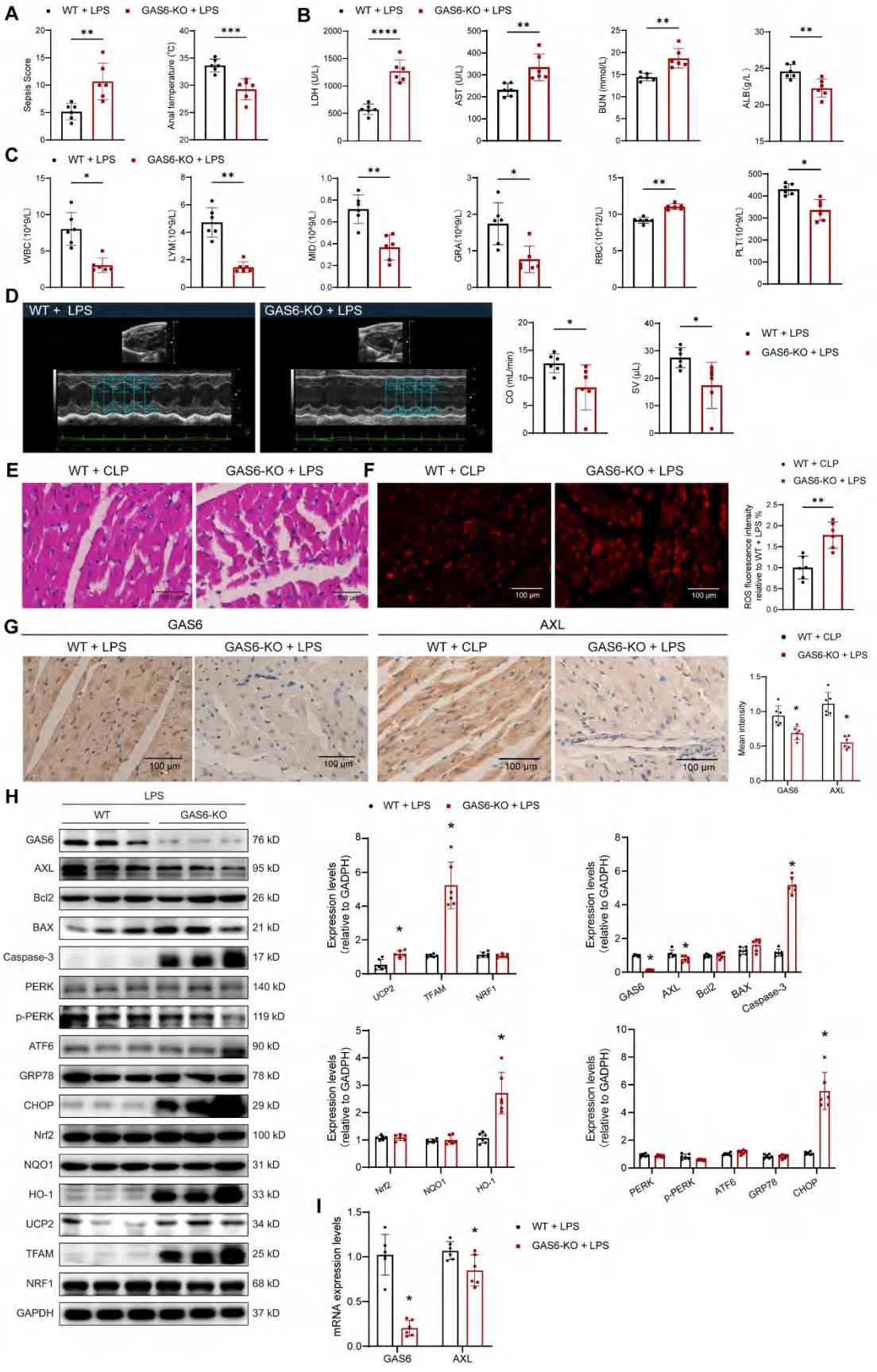


Fig. S5 GAS6 deficiency evoked deterioration of systemic biometrics, cardiac structure and

function in LPS mice. (A) The sepsis score and anal temperature in mice 8 h following LPS; **(B)** Blood biochemical parameters in mice 8 h following LPS; **(C)** Blood routine parameters in mice 8 h following LPS; Representative and quantified (CO and SV) echocardiographic results of the long **(D)** axis in mice 8 h following LPS; **(E)** Representative images of H&E staining in myocardia 8 h following LPS； **(F)** Representative images of DHE staining and quantitative analysis in myocardia 8 h following LPS; **(G)** Representative images of GAS6 and AXL IHC staining, and quantitative analysis of IHC staining in myocardia 8 h following LPS； **(H)** Representative and pooled Western blot analysis of myocardial GAS6, AXL, Bcl2, BAX, Caspase-3, PERK, p-PERK, ATF6, GRP78, CHOP, Nrf2, NQO1, HO-1, UCP2, TFAM and NRF1 in mice 8 h after LPS; and **(I)** qRT-PCR analysis of myocardial *GAS6* and *AXL* mRNA in mice 8 h after LPS. Mean ± SD. n=6 per group. $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$ vs. WT-LPS.

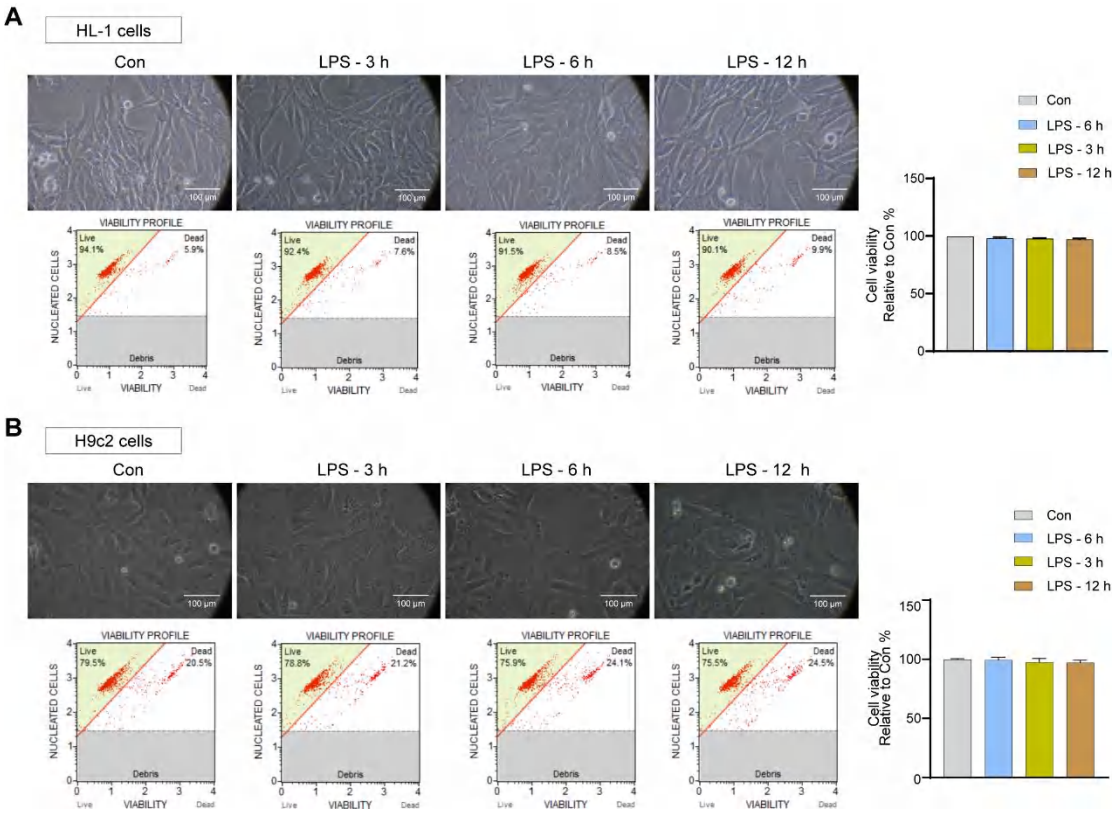


Fig. S6 The construction of sepsis models *in vitro*. (A) Cell viability in HL-1 cells 3, 6, and 12 h following LPS stimulation; and **(B)** Cell viability in H9c2 cells 3, 6, and 12 h following LPS stimulation. n=6 per group, Mean ± SD. $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$ vs. Con.

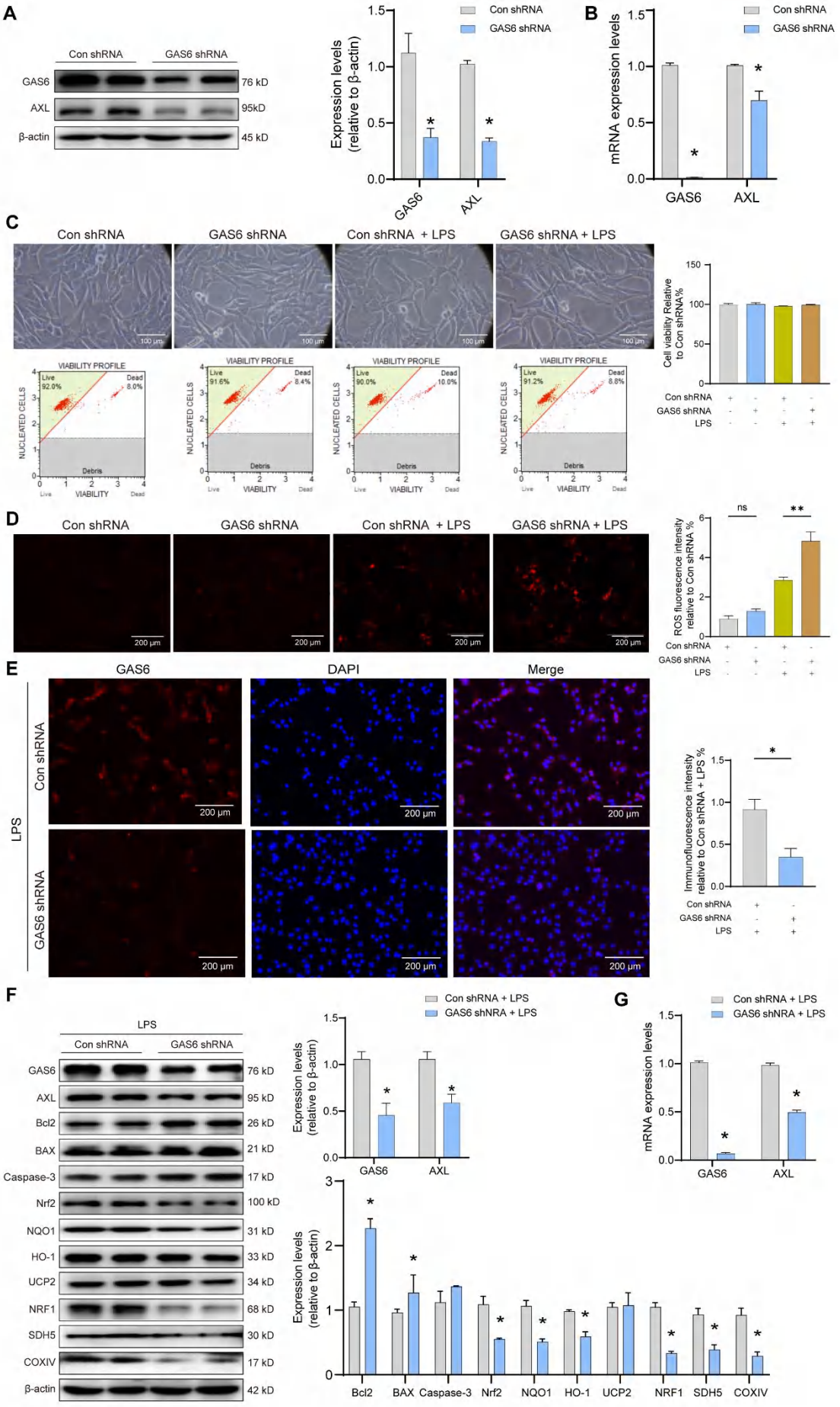

A
Con shRNA
GAS6 shRNA
GAS6
AXL
β-actin
76 kD
95kD
45 kD
Expression levels (relative to β-actin)
B
mRNA expression levels
C
Con shRNA
GAS6 shRNA
Con shRNA + LPS
GAS6 shRNA + LPS
VIABILITY PROFILE
Live 92.0%
Dead 8.0%
Live 91.6%
Dead 8.4%
Live 90.0%
Dead 10.0%
Live 91.2%
Dead 8.8%
NUCLEATED CELLS
VIABILITY
Debris
Cell viability Relative to Con shRNA%
D
ROS fluorescence intensity relative to Con shRNA %
ns
**
E
GAS6
DAPI
Merge
LPS
Immunofluorescence intensity relative to Con shRNA + LPS %
F
Bcl2
BAX
Caspase-3
Nrf2
NQO1
HO-1
UCP2
NRF1
SDH5
COXIV
95 kD
26 kD
21 kD
17 kD
100 kD
31 kD
33 kD
34 kD
68 kD
30 kD
17 kD
42 kD
Con shRNA + LPS
GAS6 shNRA + LPS
G

Fig. S7 GAS6 deficiency aggravated LPS injury in HL-1 cells. **(A)** Representative and pooled Western blot analysis of GAS6 and AXL in HL-1 cells with GAS6 shRNA; **(B)** qRT-PCR analysis of *GAS6* and *AXL* mRNA in HL-1 cells with GAS6 shRNA; (**C**) Representative cell morphology images and cell viability of LPS-stimulated HL-1 cells with GAS6 deficiency; (**D**) Intracellular ROS levels of LPS-stimulated HL-1 cells with GAS6 deficiency; (**E**) Representative and pooled immunofluorescence photographs for GAS6 (red) and DAPI (blue) in LPS-stimulated HL-1 cells with GAS6 deficiency; (**F**) Representative and pooled Western blot analysis of GAS6, AXL, Bcl2, BAX, Caspase-3, Nrf2, NQO1, HO-1, UCP2, NRF1, SDH5 and COXIV following LPS-stimulated in HL-1 cells with GAS6 deficiency; and (**G**) qRT-PCR analysis of GAS6 and AXL mRNA following LPS-stimulated in HL-1 cells with GAS6 deficiency. Mean ± SD. n=6 per group, **P*<0.05, ***P*<0.01, ****P*<0.001 vs. Con shRNA (panel A-B) or Con shRNA-LPS (panel C-F).

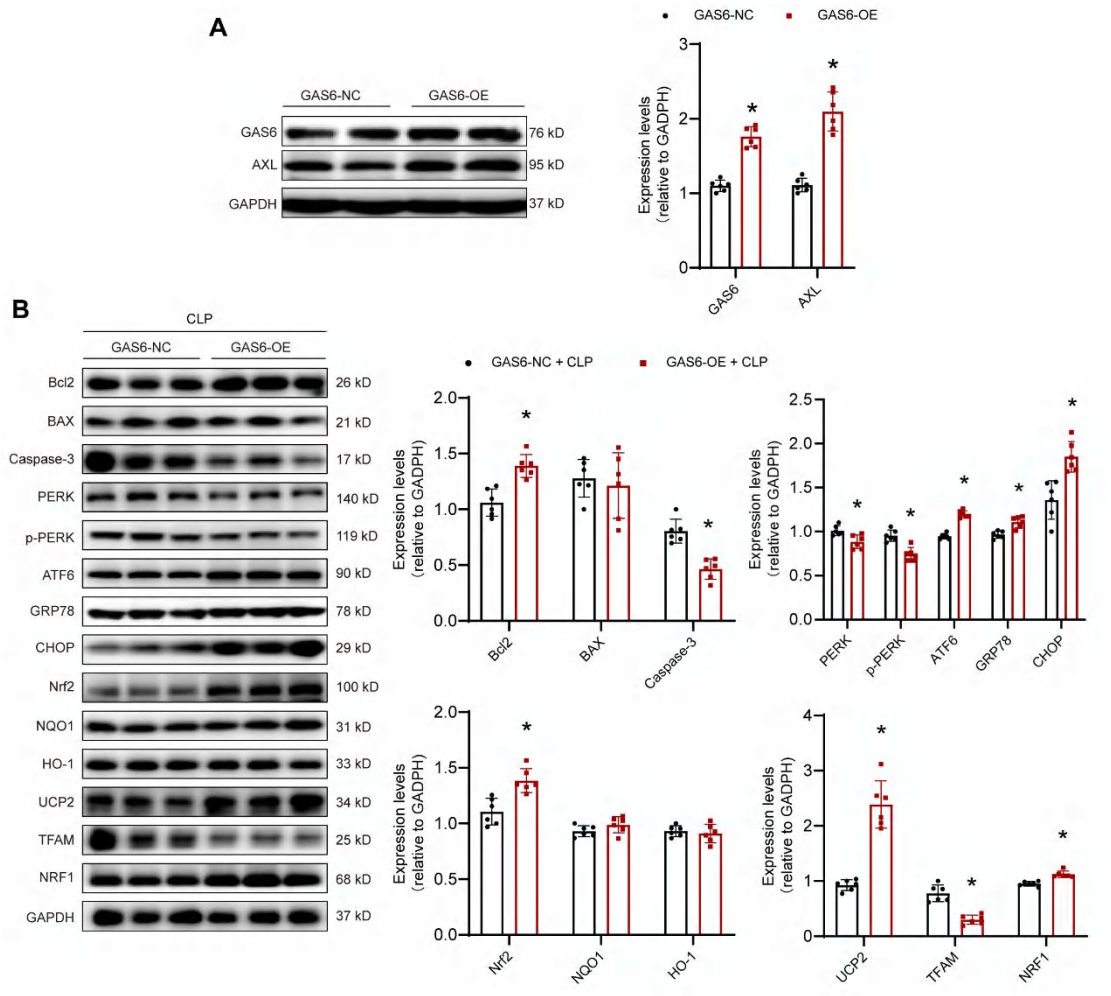


Fig. S8 Identification of GAS6 overexpression in mice and the effects of GAS6 overexpression *in vivo* on the CLP-induced various pathways. (A) Representative and pooled Western blot analysis of myocardial GAS6 and AXL in mice with GAS6-OE; and **(B)** Representative and pooled Western blot analysis of myocardial Bcl2, BAX, Caspase-3, PERK, p-PERK, ATF6, GRP78, CHOP, Nrf2, NQO1, HO-1, UCP2, TFAM and NRF1 in CLP-injured mice with GAS6-OE. Mean ± SD. n=6 per group, $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$ vs. GAS6-NC (panel A) or GAS6-NC-CLP (panel B).

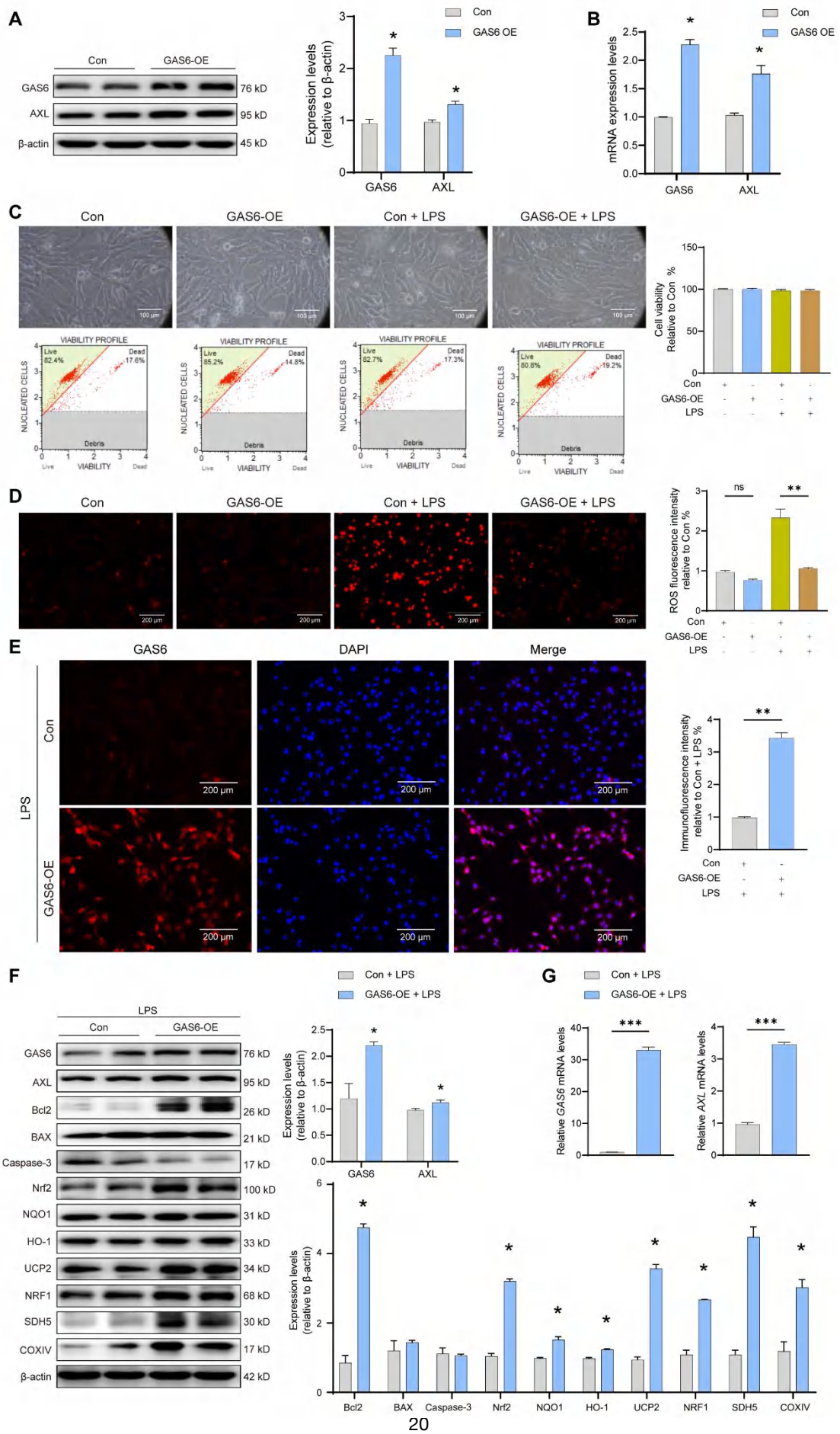

A
Con
GAS6-OE
GAS6
AXL
β-actin
76 kD
95 kD
45 kD
Expression levels (relative to β-actin)
Con
GAS6 OE
GAS6
AXL
B
mRNA expression levels
C
Con
GAS6-OE
Con + LPS
GAS6-OE + LPS
VIABILITY PROFILE
NUCLEATED CELLS
VIABILITY
Cell viability Relative to Con %
D
ROS fluorescence intensity relative to Con %
ns
E
GAS6
DAPI
Merge
LPS
Immunofluorescence intensity relative to Con + LPS %
F
Bcl2
BAX
Caspase-3
Nrf2
NQO1
HO-1
UCP2
NRF1
SDH5
COXIV
G
Relative GAS6 mRNA levels
Relative AXL mRNA levels

Fig. S9 GAS6 overexpression alleviated LPS injury in HL-1 cells. (A) Representative and pooled Western blot analysis of GAS6 and AXL in HL-1 cells with GAS6-OE; **(B)** qRT-PCR analysis of *GAS6* and *AXL* mRNA in HL-1 cells with GAS6-OE; **(C)** Representative cell morphology images and cell viability of LPS-stimulated HL-1 cells with GAS6-OE; **(D)** Intracellular ROS levels of LPS-stimulated HL-1 cells with GAS6-OE; **(E)** Representative and pooled immunofluorescence photographs for GAS6 (red) and DAPI (blue) in LPS-stimulated HL-1 cells with GAS6-OE; **(F)** Representative and pooled Western blot analysis of GAS6, AXL, Bcl2, BAX, Caspase-3, Nrf2, NQO1, HO-1, UCP2, NRF1, SDH5 and COXIV in LPS-stimulated HL-1 cells with GAS6-OE; and **(G)** qRT-PCR analysis of *GAS6* and *AXL* mRNA in LPS-stimulated HL-1 cells with GAS6-OE. Mean ± SD. n=6 per group, $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$ vs. Con (panel A-B) or Con-LPS (panel C-G).

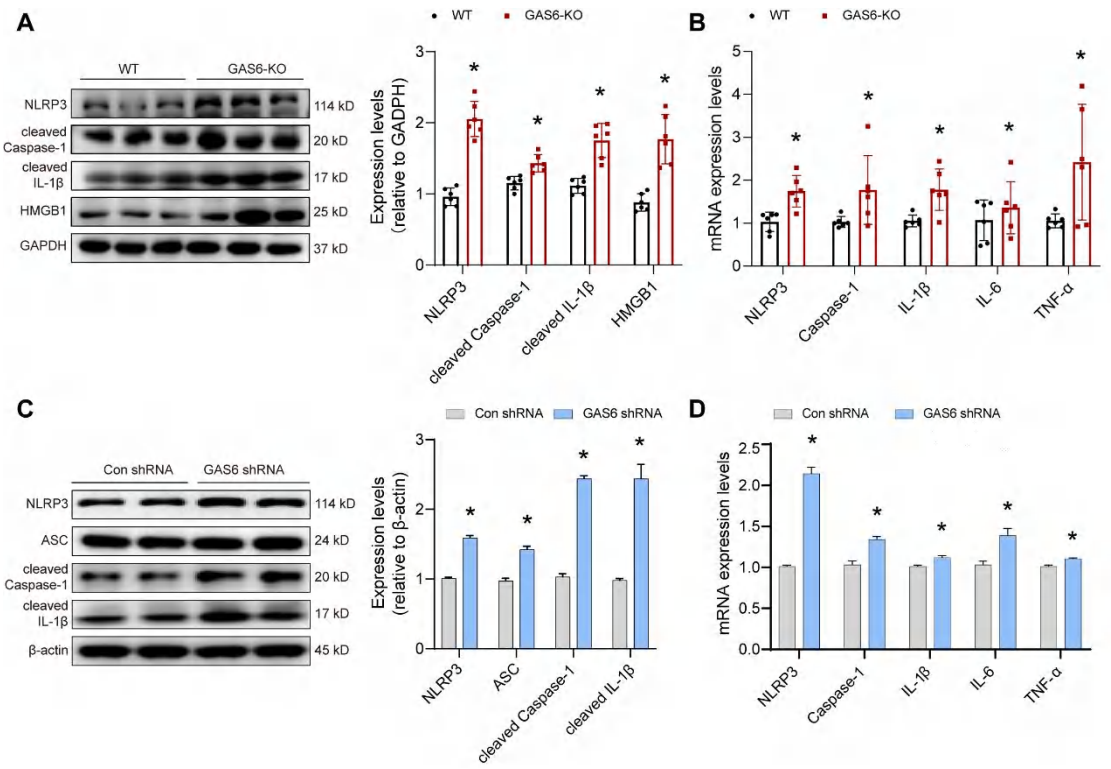


Fig. S10 Effects of GAS6 deficiency alone on the production of NLRP3-mediated pro-inflammatory mediators *in vivo* or *in vitro*. (A) Representative and pooled Western blot analysis of myocardial NLRP3, cleaved Caspase-1, cleaved IL-1β and HMGB1 in mice with GAS6 deficiency; **(B)** qRT-PCR analysis of myocardial *NLRP3, Caspase-1, IL-1β, IL-6* and *TNF-α* mRNA in mice with GAS6 deficiency; **(C)** Representative and pooled Western blot analysis of NLRP3, ASC, cleaved Caspase-1 and cleaved IL-1β in HL-1 cells with GAS6 shRNA; **(D)** qRT-PCR analysis of *NLRP3, Caspase-1, IL-1β, IL-6* and *TNF-α* mRNA in HL-1 cells with GAS6 shRNA. Mean ± SD. n = 6 per group, $^{*}P<0.05$ vs. WT (panel A-B) or Con shRNA (panel C-D).

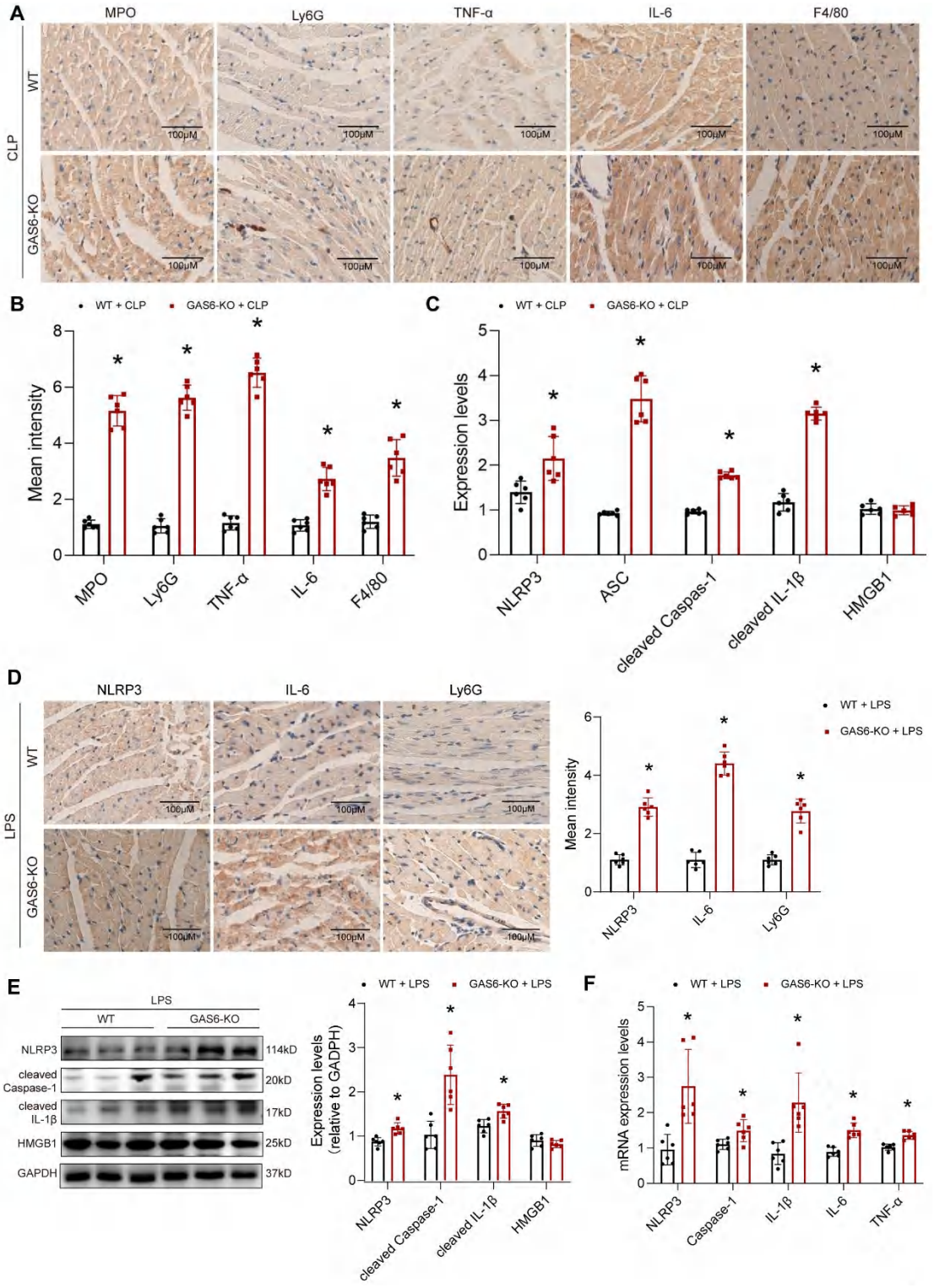


Fig. S11 Effects of GAS6 knockout on NLRP3-related pro-inflammatory mediators in CLP or LPS mice. (A-B) Representative and pooled immunohistochemistry staining results of myocardial MPO, Ly6G, TNF-α, IL-6 and F4/80 in mice with GAS6-KO 8 h following CLP; **(C)** Pooled Western blot analysis of myocardial NLRP3, ASC, cleaved Caspase-1, cleaved IL-1β and

HMGB1 in mice with GAS6-KO 8 h after CLP; **(D)** Representative and pooled IHC staining results of myocardial NLRP3, IL-6 and Ly6G in mice with GAS6-KO 8 h following LPS; **(E)** Representative and pooled Western blot analysis of myocardial NLRP3, cleaved Caspase-1, cleaved IL-1β and HMGB1 in mice with GAS6-KO 8 h after LPS injection; and **(F)** qRT-PCR analysis of myocardial NLRP3, Caspase-1, IL-1β, IL-6 and TNF-α mRNA in mice with GAS6-KO 8 h after LPS injection. Mean ± SD. n=6 per group, **P*<0.05 vs. WT-CLP (panel A-C) or WT-LPS (panel D-F).

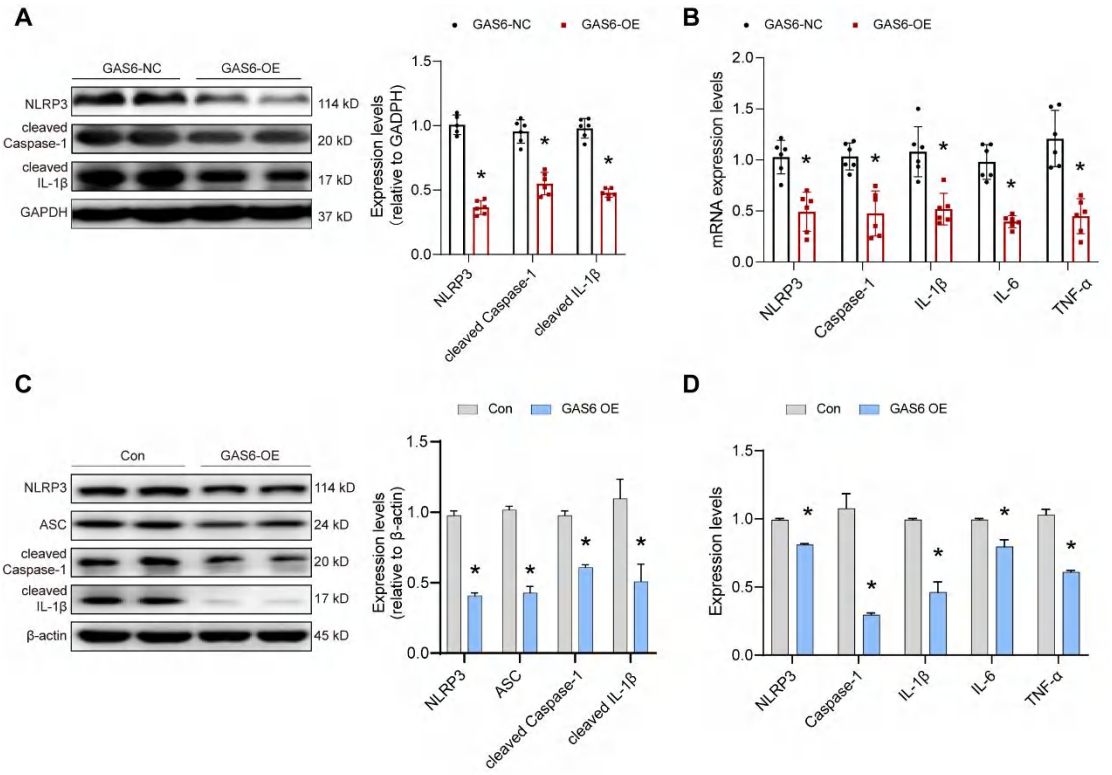


Fig. S12 Effects of GAS6 overexpression alone on the production of NLRP3-mediated pro-inflammatory mediators *in vivo* or *in vitro*. (A) Representative and pooled Western blot analysis of myocardial NLRP3, cleaved Caspase-1 and cleaved IL-1β in mice with GAS6-OE; and **(B)** qRT-PCR analysis of myocardial NLRP3, Caspase-1, IL-1β, IL-6 and TNF-α mRNA in mice with GAS6-OE. **(C)** Representative and pooled Western blot analysis of NLRP3, ASC, cleaved Caspase-1 and cleaved IL-1β in HL-1 cells with GAS6-OE; and **(D)** qRT-PCR analysis of *NLRP3, Caspase-1, IL-1β, IL-6* and *TNF-α* mRNA in HL-1 cells with GAS6-OE. Mean ± SD. n = 6 per group, $^{*}P<0.05$ vs. GAS6-NC (panel A-B) or Con (panel C-D).

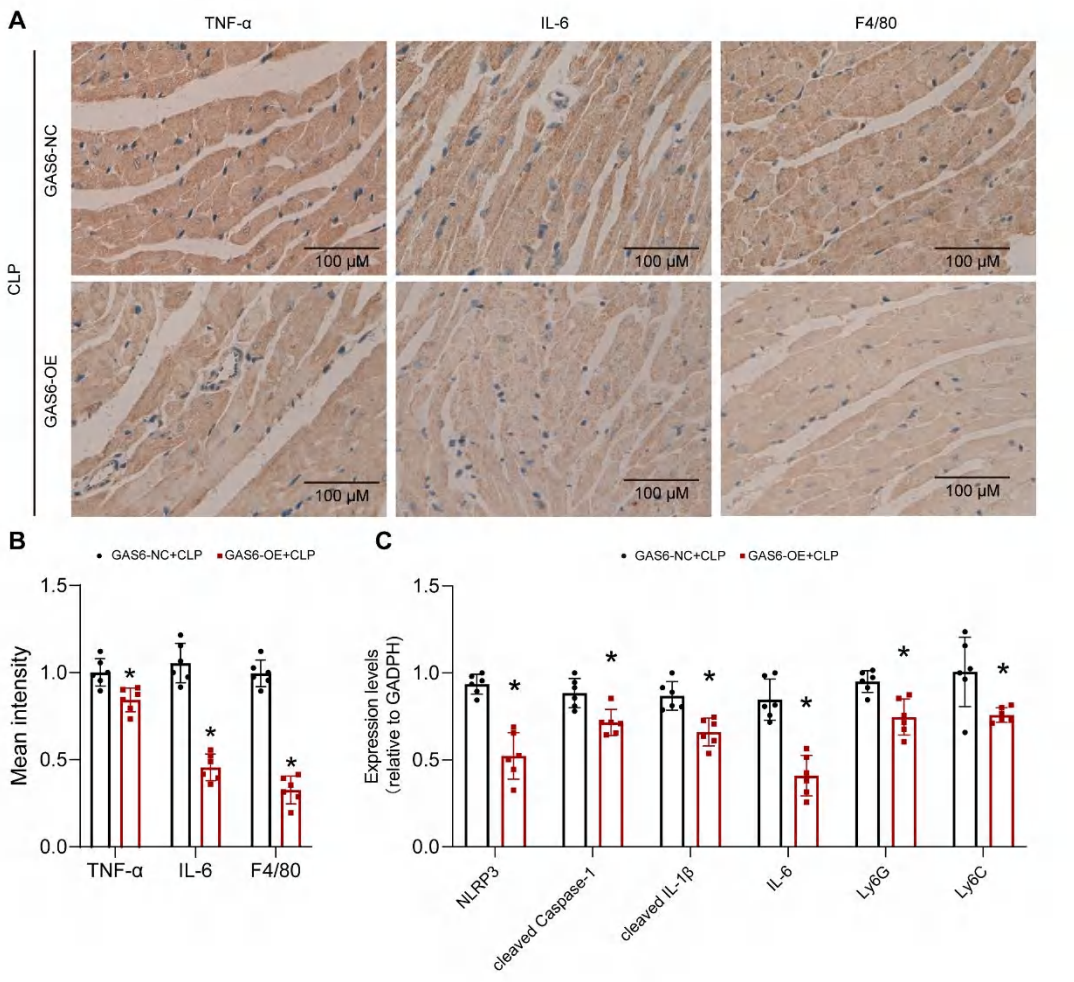
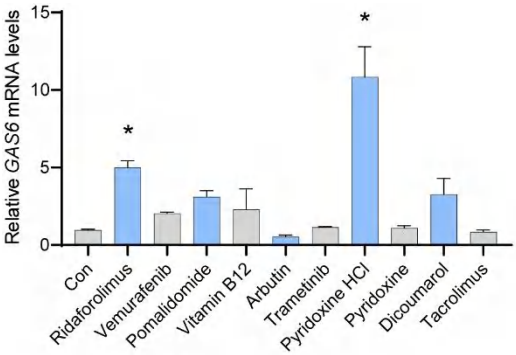
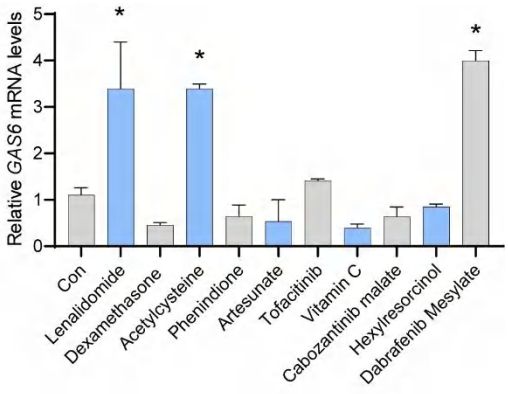
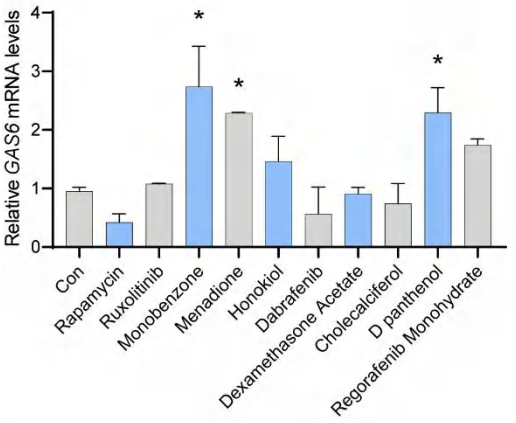
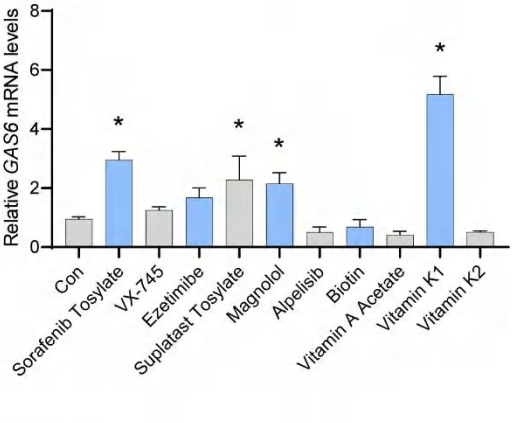


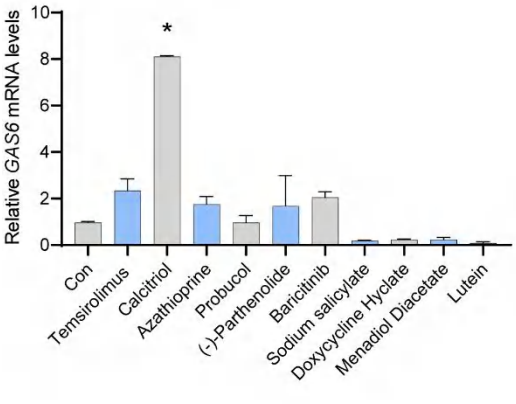
Fig. S13 GAS6 overexpression down-regulated levels of NLRP3-mediated pro-inflammatory mediators in CLP-injured mice. (A-B) Representative and pooled IHC staining results of myocardial TNF-α, IL-6 and F4/80 in mice with GAS6-OE 8 h following CLP; **(C)** Pooled Western blot analysis of myocardial NLRP3, cleaved Caspase-1, cleaved IL-1β, IL-6, Ly6G and Ly6C in mice with GAS6-OE 8 h after CLP. Mean ± SD. n=6 per group, $^{*}P<0.05$ vs. GAS6-NC-CLP.

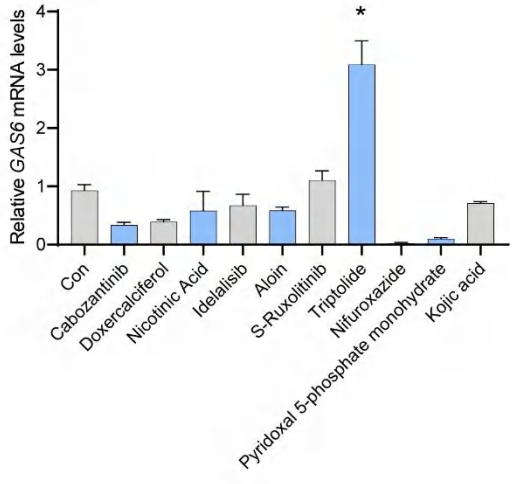

Relative GAS6 mRNA levels
15
10
5
0
*
*
Con
Ridaforolimus
Vemurafenib
Pomalidomide
Vitamin B12
Arbutin
Trametinib
Pyridoxine HCl
Pyridoxine
Dicoumarol
Tacrolimus

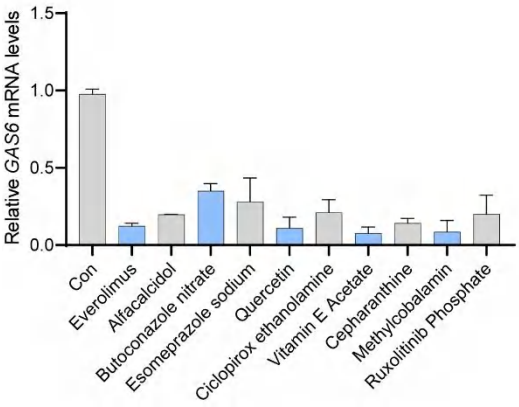

Relative GAS6 mRNA levels
5
4
3
2
1
0
*
*
*
Con
Lenalidomide
Dexamethasone
Acetylcysteine
Phenindione
Artesunate
Tofacitinib
Vitamin C
Cabozantinib malate
Hexylresorcinol
Dabrafenib Mesylate


Relative GAS6 mRNA levels
4
3
2
1
0
*
*
*
Con
Rapamycin
Ruxolitinib
Monobenzone
Menadione
Honokiol
Dabrafenib
Dexamethasone Acetate
Cholecalciferol
D panthenol
Regorafenib Monohydrate


Relative GAS6 mRNA levels
8
6
4
2
0
*
*
*
*
Con
Sorafenib Tosylate
VX-745
Ezetimibe
Suplatast Tosylate
Magnolol
Alpelisib
Biotin
Vitamin A Acetate
Vitamin K1
Vitamin K2


Relative GAS6 mRNA levels
10
8
6
4
2
0
*
Con
Temsirolimus
Calcitriol
Azathioprine
Probucol
(-)-Parthenolide
Baricitinib
Sodium salicylate
Doxycycline Hyclate
Menadiol Diacetate
Lutein


Relative GAS6 mRNA levels
4
3
2
1
0
*
Con
Cabozantinib
Doxercalciferol
Nicotinic Acid
Idelalisib
Aloin
S-Ruxolitinib
Triptolide
Nifuroxazide
Pyridoxal 5-phosphate monohydrate
Kojic acid


Relative GAS6 mRNA levels
1.5
1.0
0.5
0.0
Con
Everolimus
Alfacalcidol
Butoconazole nitrate
Esomeprazole sodium
Quercetin
Ciclopirox ethanolamine
Vitamin E Acetate
Cepharanthine
Methylcobalamin
Ruxolitinib Phosphate

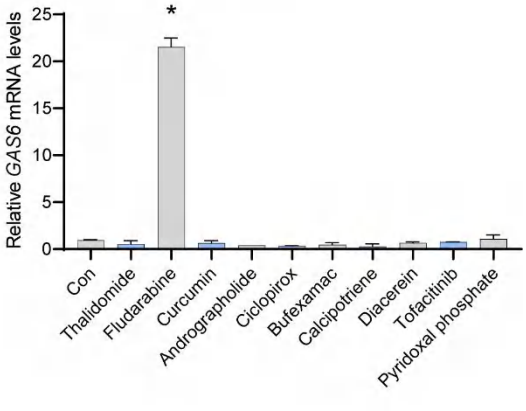

Relative GAS6 mRNA levels
25
20
15
10
5
0
*
Con
Thalidomide
Fludarabine
Curcumin
Andrographolide
Ciclopirox
Bufexamac
Calcipotriene
Diacerein
Tofacitinib
Pyridoxal phosphate

Fig. S14 Screening of GAS6 pharmacological agonists. qRT-PCR analysis of *GAS6* mRNA levels in HL-1 cells treated with 123 FDA-approved drugs for 3 h. Mean ± SD. n=6 for each group, $^{*}P<0.05$ vs. Con.

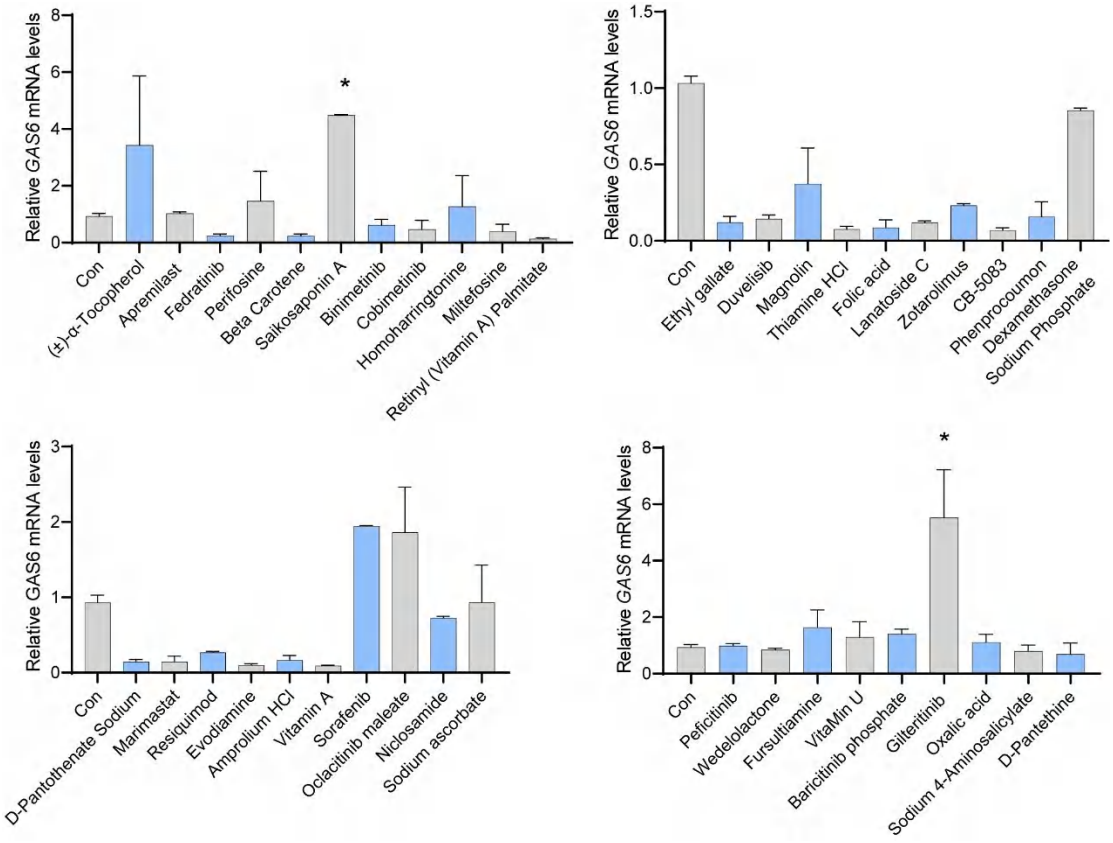


Fig. S15 Screening of GAS6 pharmacological agonists. qRT-PCR analysis of *GAS6* mRNA levels in HL-1 cells treated with 123 FDA-approved drugs for 3 h. Mean ± SD. n=6 for each group, $^{*}P<0.05$ vs. Con.

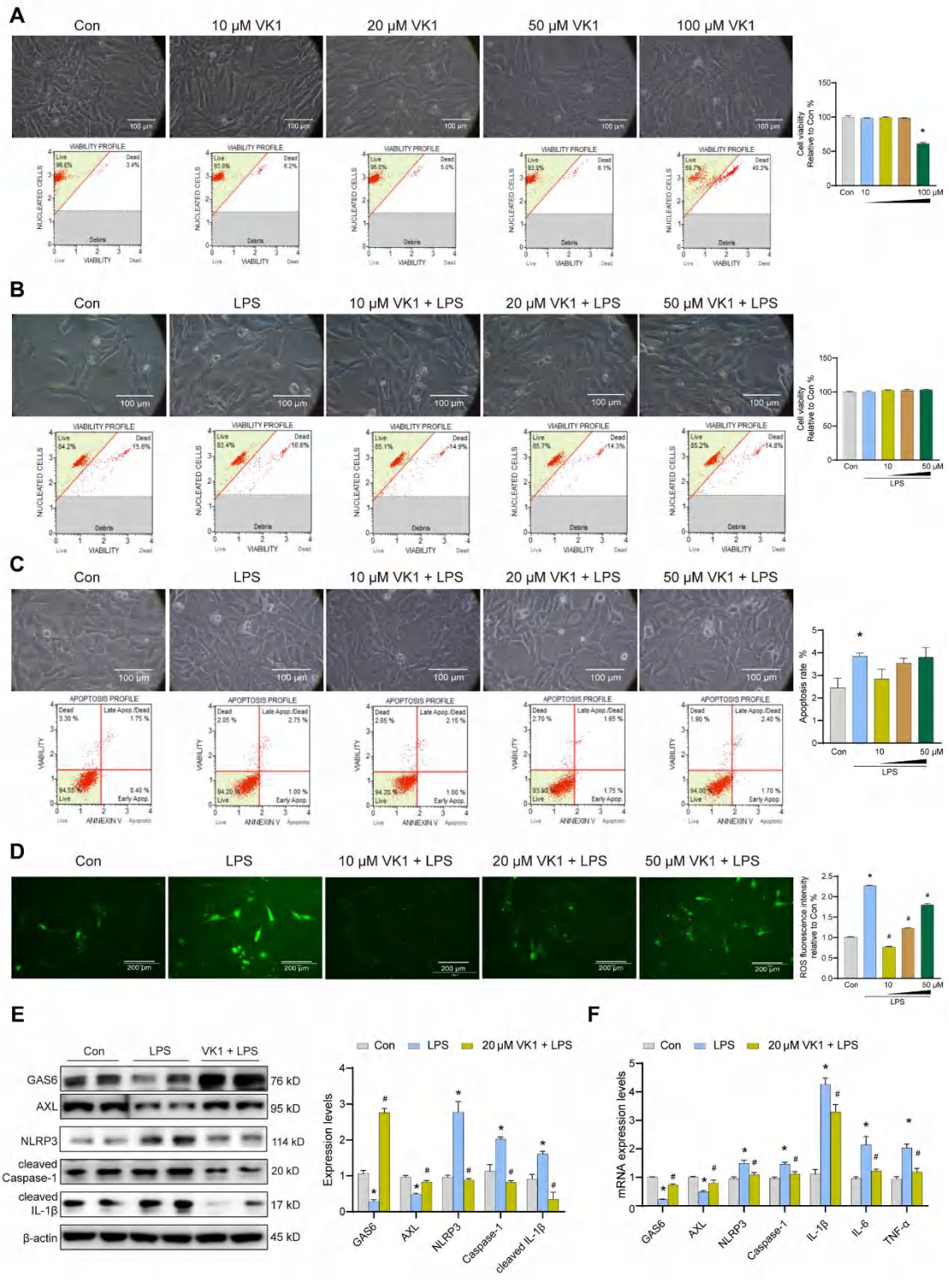


Fig. S16 VK1 alleviated septic injury in HL-1 cells through a GAS6-dependent manner. (A) Representative cell morphology images and cell viability of HL-1 cells treated with VK1 for 24 h, n=6; (**B**) Cell viability in HL-1 cells treated with VK1 at different concentrations (10, 20 or 50 μM) for 3 h prior to exposure to LPS, n=6; (**C**) Apoptosis rates of VK1 and LPS-treated HL-1 cells; (**D**)

Intracellular ROS levels of VK1 and LPS-treated HL-1 cells; (**E**) Representative and pooled Western blot analysis of GAS6, AXL, NLRP3, cleaved Caspase-1 and cleaved IL-1β in VK1 and LPS-treated HL-1 cells; and **(F)** qRT-PCR analysis of *GAS6, AXL, NLRP3, Caspase-1, IL-1β, IL-6* and *TNF-α* mRNA in VK1 and LPS-treated cells; n=6. Mean ± SD. **P*<0.05 vs. Con (panel A). or vs. LPS (panel B-F).

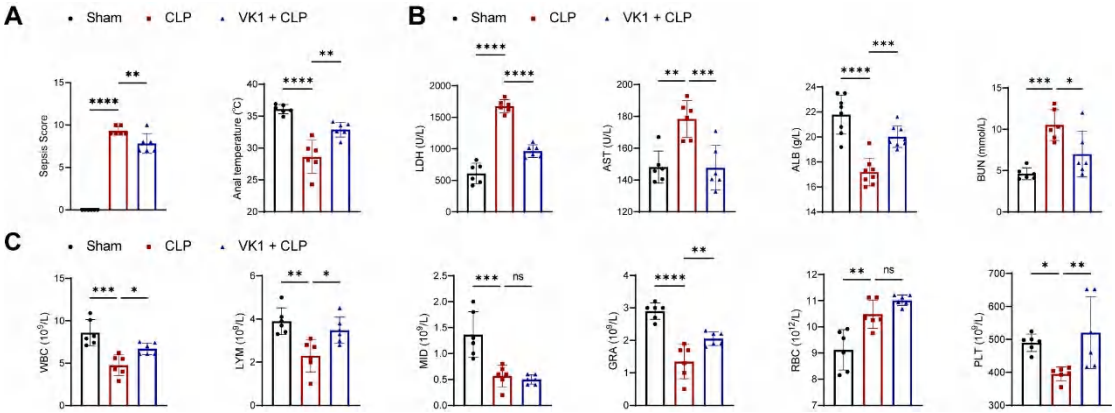


Fig. S17 Effects of VK1 on the sepsis score, anal temperature, and systematical status of CLP mice. (A) Sepsis score and anal temperature in mice subject to VK1 pretreatment and CLP operation **(B)** Blood biochemical parameters in mice subject to VK1 pretreatment and CLP operation; **(C)** Blood routine parameters in mice subject to VK1 pretreatment and CLP operation. Mean ± SD. $^{*}P$<0.05 vs. Sham.

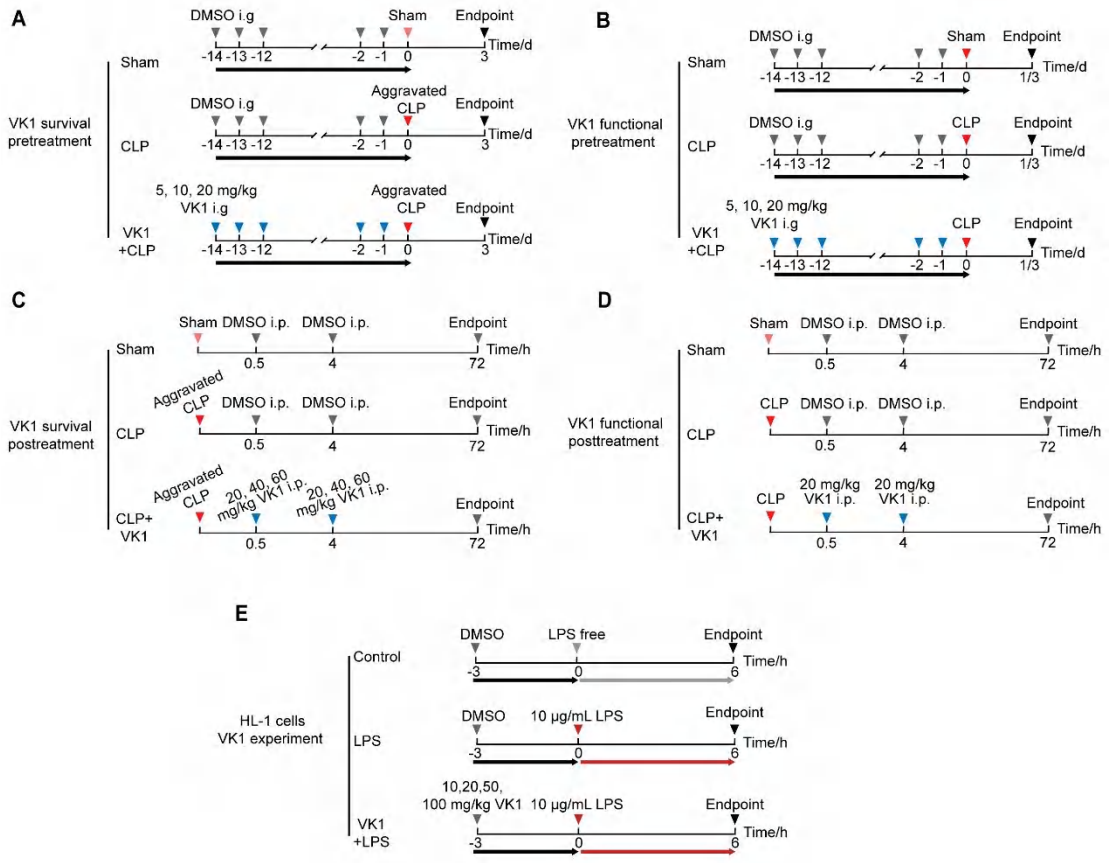


Fig. S18 Experiment timeline. (A) Experimental design of survival rate in CLP mice pretreated with VK1; (**B**) Experimental design of functional analysis in VK1-pretreated CLP mice; **(C)** Experimental design of survival rate in CLP mice post-treated with VK1; (**D**) Experimental design of functional analysis in mice with VK1 post-treated; and (**E**) Experimental design of VK1-treated HL-1 cells.