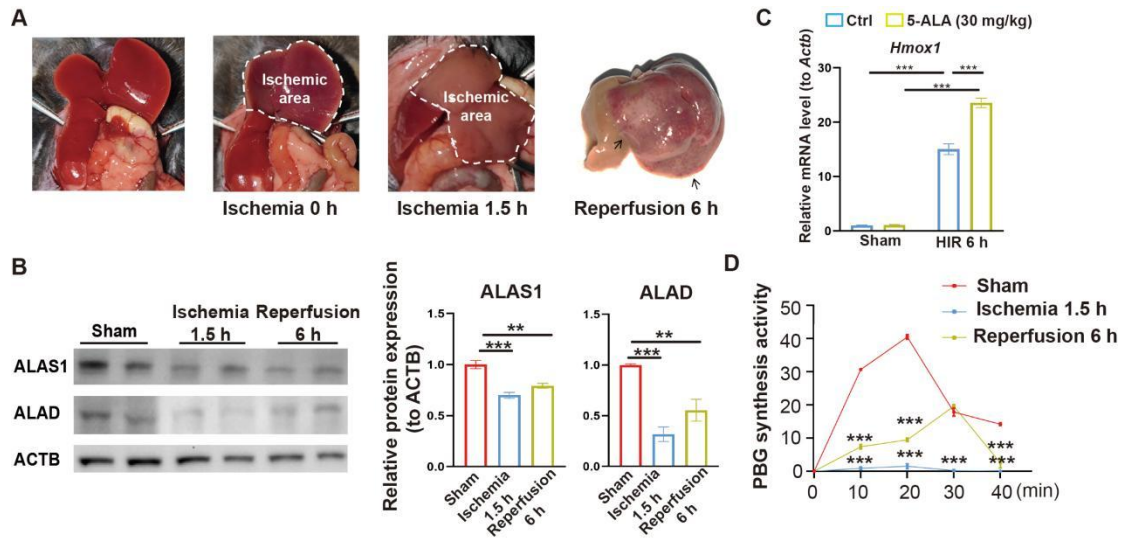


1 **Supplemental Figures and legends**



2

3 **Figure S1. 5-ALA metabolic pathway in mouse HIR model. Related to Figure 1.**

4 (A) Representative images demonstrating the mouse HIR operation (arrows denote
5 hepatic areas with HIR injury).

6 (B) Representative western blots on the hepatic content of key enzymes ALAS1 and
7 ALAD in the 5-ALA metabolic pathway from mice at indicated conditions (n = 4).
8 Their signal intensity is normalized to that of ACTB.

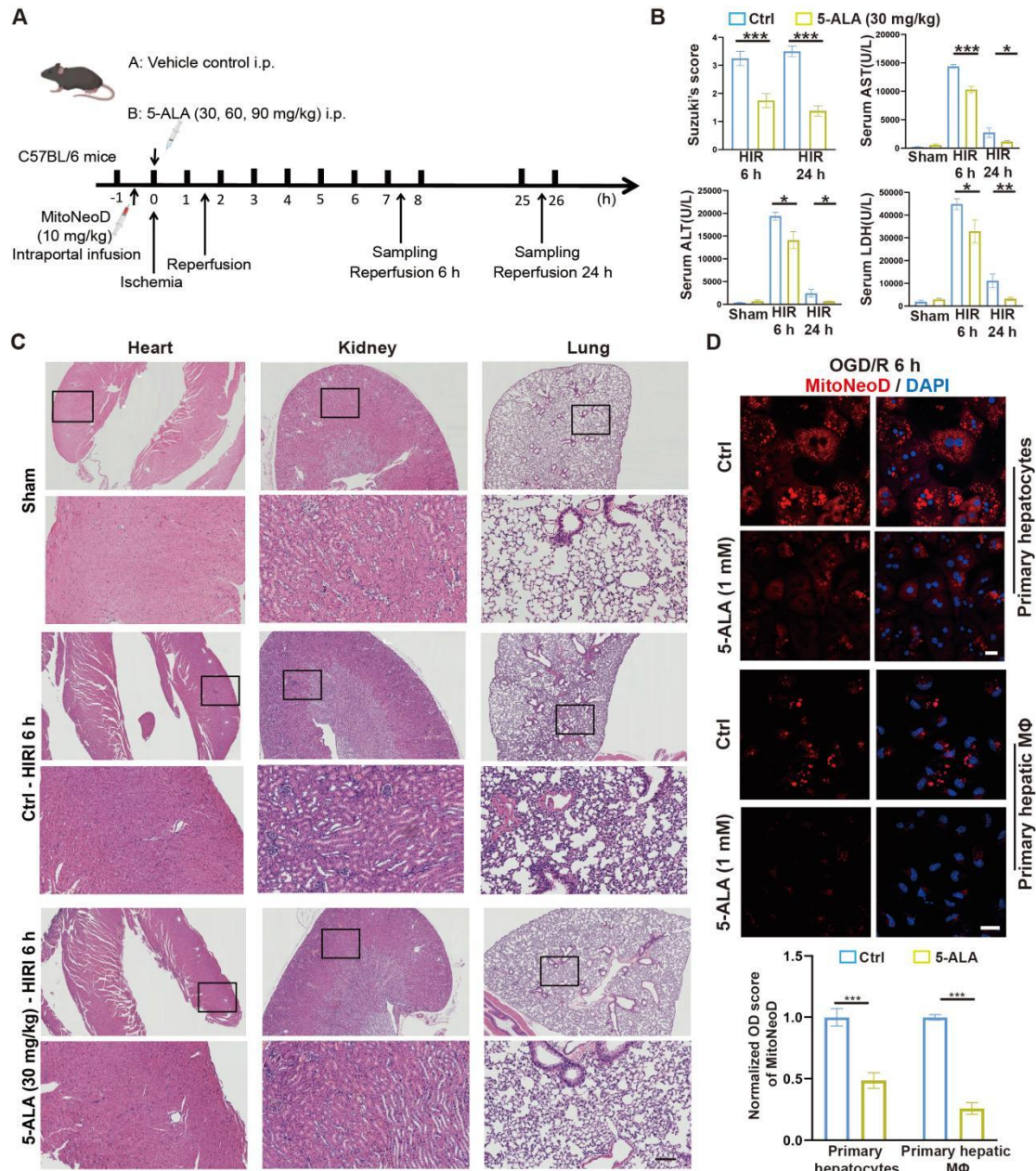
9 (C) Relative mRNA levels of *Hmox1* in mouse livers at indicated conditions
10 normalized to that of *Actb* (n = 6).

11 (D) Activity of ALAD at indicated conditions (n = 3).

12 Results are presented as mean \pm SEM. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ by
13 one-way ANOVA (B), (C) and (D).

14

15



16

17 **Figure S2. Supplemented 5-ALA relieves HIR-induced injury and mitochondrial**
 18 **ROS overproduction. Related to Figure 2.**

19 (A) Outline of the mouse HIR experimental procedures and conditions.

20 (B) Liver injury indicators Suzuki's score, AST, ALT and LDH levels in mice at

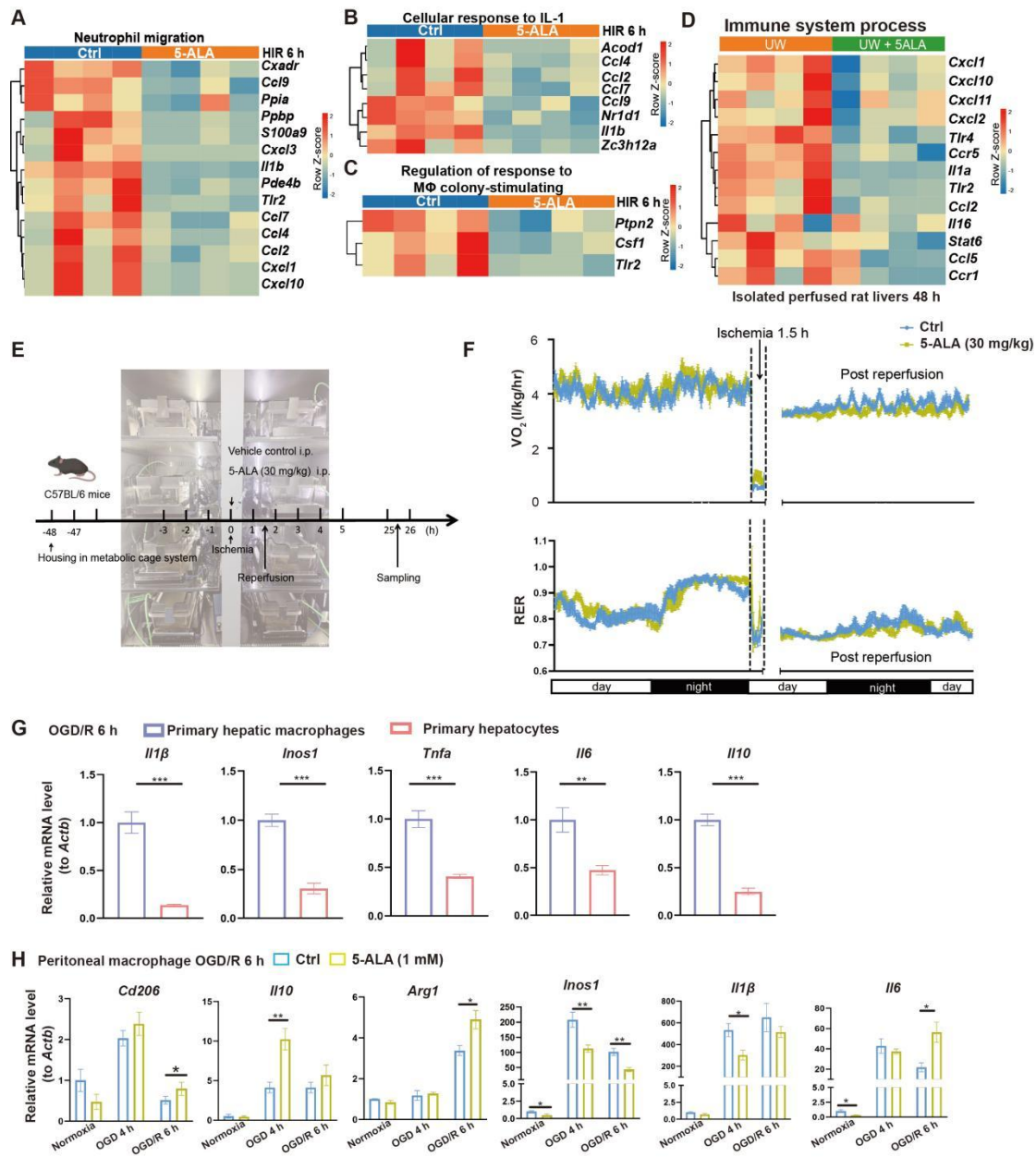
21 indicated conditions (n = 8 per group).

22 (C) Representative H&E staining of heart, kidney and lung sections from mice at
23 indicated conditions. No overt abnormality was found in the 5-ALA treatment group
24 (scale bar = 0.1 mm).

25 (D) MitoNeoD (red) and DAPI (blue) staining to evaluate mitochondrial ROS
26 overproduction in mouse primary hepatocytes and hepatic macrophages at annotated
27 conditions (n = 5 experiments, scale bar = 10 μ m).

28 Results are presented as mean \pm SEM. * P < 0.05, ** P < 0.01, *** P < 0.001 by
29 two-tailed Student's t tests (D) or one-way ANOVA (B).

30



31

32 **Figure S3. 5-ALA modulates mouse hepatic metabolism and immune responses**

33 **following HIR. Related to Figure 3.**

34 (A) Heatmap of differentially expressed genes (DEGs) related to neutrophil migration

35 (GO:1990266) in mouse liver samples at annotated conditions (n = 4 per group).

36 (B) Heatmap of DEGs related to cellular response to IL-1 (GO:0071347) in mouse

37 liver samples at indicated conditions (n = 4 per group).

38 (C) Heatmap of DEGs related to regulation of response to macrophage
39 colony-stimulating factor (GO:1903969) in mouse liver samples at indicated
40 conditions (n = 4 per group). Red, high relative expression; blue, low relative
41 expression.

42 (D) Heatmap of DEGs related to immune system process (GO:0002376) in isolated
43 perfused rat liver at indicated conditions (n = 4). Red, high relative expression; blue,
44 low relative expression.

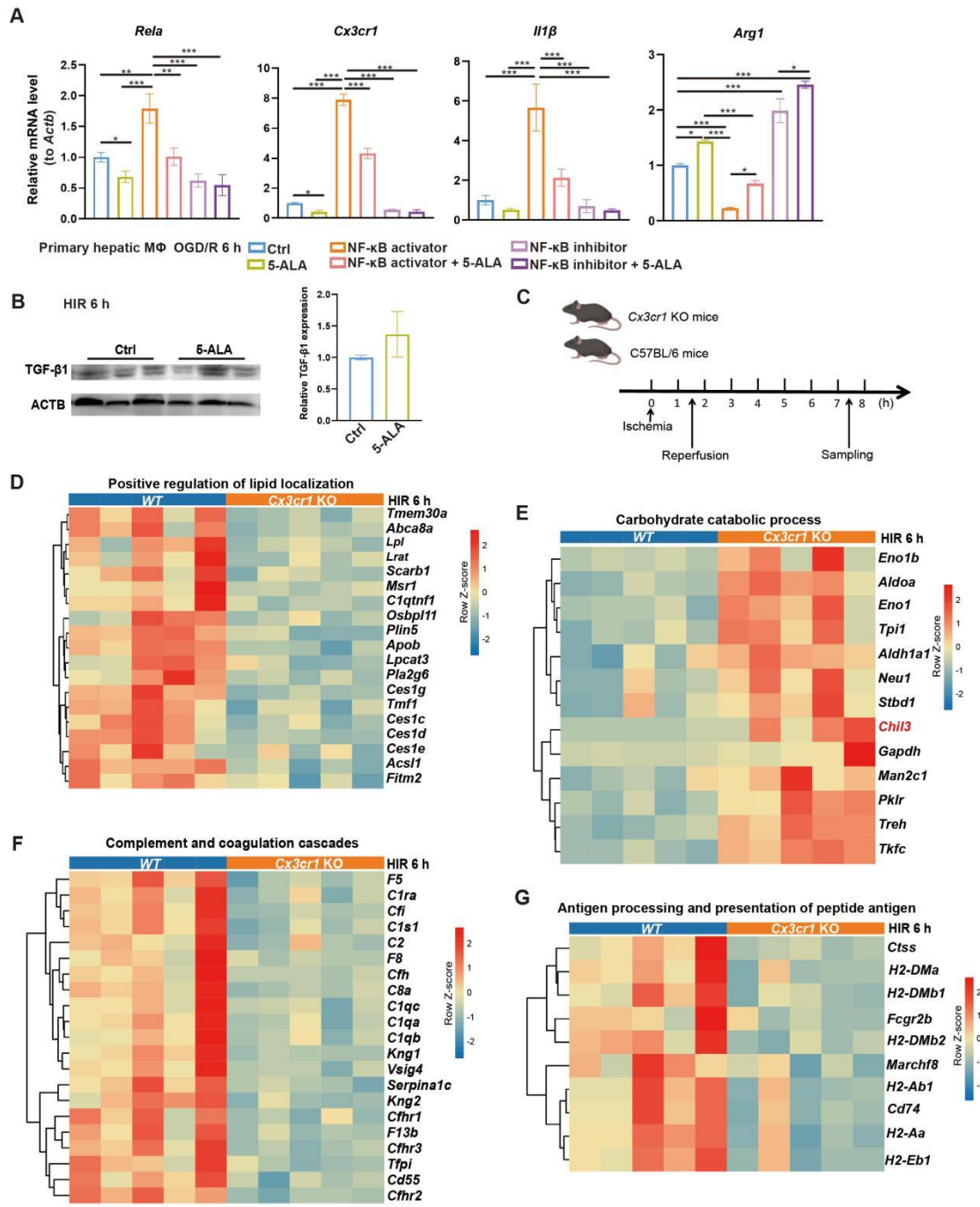
45 (E) Outline of the HIR experimental conditions and setup of the mouse metabolic
46 cage system.

47 (F) Representative results of oxygen consumption rates (OCR, VO₂) and respiratory
48 exchange ratio (RER) in control and 5-ALA-treated mice measured as indicated with
49 the mouse metabolic cage system. Values normalized to the body weight of each
50 mouse (n = 6 per group).

51 (G) Relative mRNA expression of inflammatory cytokines (*Il1β*, *Inos1*, *Tnfa*, *Il6* and
52 *Il10*) of in mouse primary macrophages and hepatocytes 6 h after OGD/R (n = 6 per
53 group). The mRNA level of each gene is normalized to that of *Actb*.

54 (H) Relative mRNA expression of macrophagic M1-enriched genes (*Cd206*, *Il10*,
55 *Arg1*) and M2-enriched genes (*Inos1*, *Il1β*, *Il6*) in mouse peritoneal macrophage
56 cultures at indicated conditions (n = 6 per group). The mRNA level of each gene is
57 normalized to that of *Actb*.

58 Results are presented as mean ± SEM. **P* < 0.05, ***P* < 0.01, ****P* < 0.001 by
59 two-tailed Student's *t* tests (G) or one-way ANOVA (H).



60

61 **Figure S4. CX3CR1 deficiency profoundly affects hepatic metabolism and**
 62 **immune responses as downstream effects of 5-ALA treatment during mouse HIR.**

63 **Related to Figure 4.**

64 (A) Relative mRNA expression of *Rela*, *Cx3cr1*, *Il1β* and *Arg1* in mouse primary
 65 hepatic macrophages at indicated conditions (NF-κB activator: 8 μg/mL betulinic acid,

66 NF- κ B inhibitor: 5 μ M BAY-11-7082, 5-ALA: 1 mM, n = 6 per group). The mRNA
67 level of each gene is normalized to that of *Actb*.

68 (B) Representative western blots of TGF- β 1 in mouse livers at indicated conditions (n
69 = 3). Their signal intensity is normalized to that of ACTB.

70 (C) Outline of the HIR experimental procedures in *WT* and *Cx3cr1* KO mice.

71 (D) Heatmap of expressed gene related to positive regulation of lipid localization
72 (GO:1905954) differentially regulated between *WT* and *Cx3cr1* KO mouse liver 6 h
73 after HIR (n = 5 per group). Red, high relative expression; blue, low relative
74 expression.

75 (E) Heatmap of expressed gene related to carbohydrate catabolic process
76 (GO:0016052) differentially regulated between *WT* and *Cx3cr1* KO mouse liver 6 h
77 after HIR (n = 5 per group). Red, high relative expression; blue, low relative
78 expression.

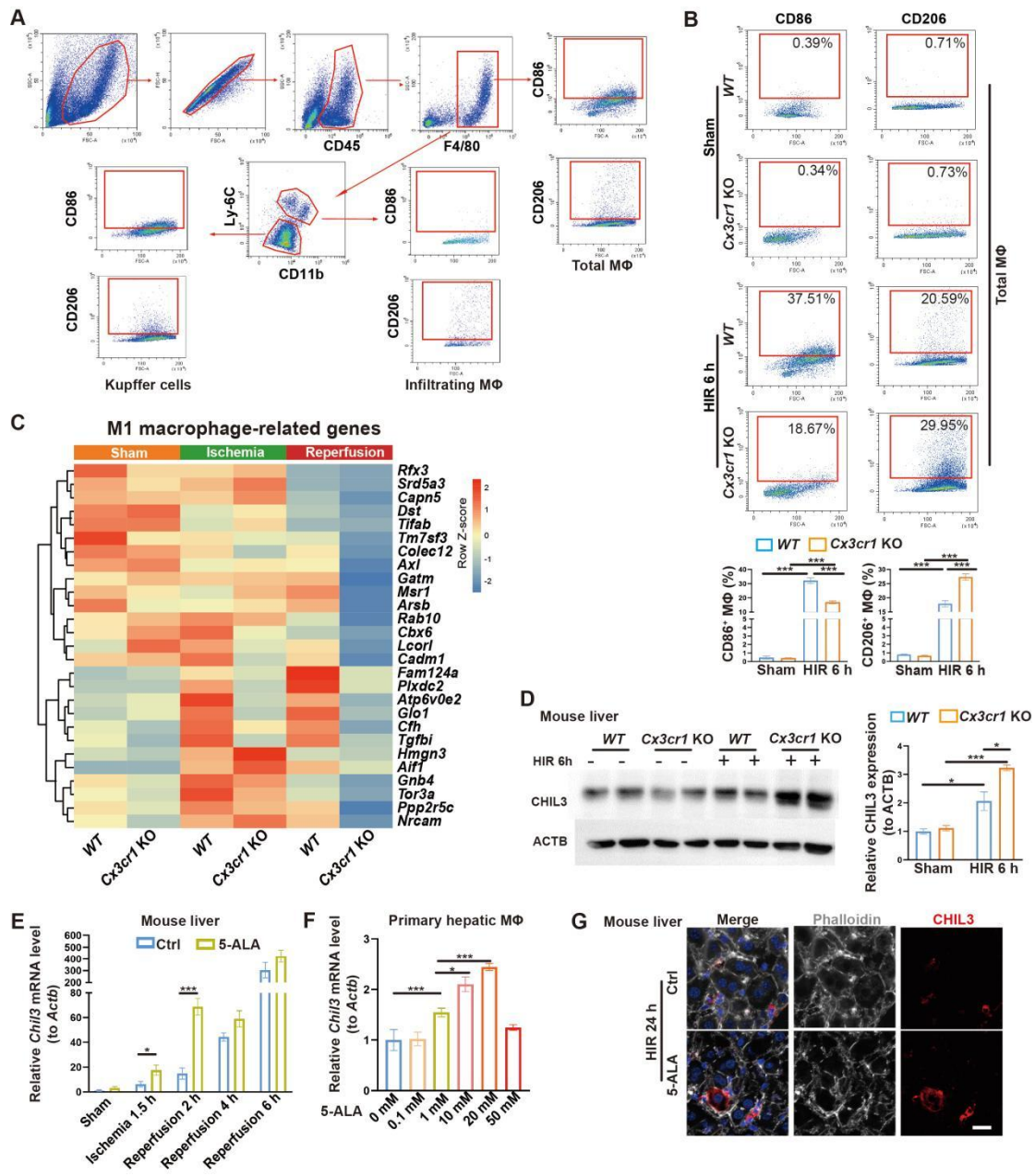
79 (F) Heatmap of expressed genes related to complement and coagulation cascades
80 (MMU04610) differentially regulated between *WT* and *Cx3cr1* KO mouse liver 6 h
81 after HIR (n = 5 per group). Red, high relative expression; blue, low relative
82 expression.

83 (G) Heatmap of expressed genes related to antigen processing and presentation of
84 peptide antigen (GO:0002495) differentially regulated between *WT* and *Cx3cr1* KO
85 mouse liver 6 h after HIR (n = 5 per group). Red, high relative expression; blue, low
86 relative expression.

87 Results are presented as mean \pm SEM. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ by

88 two-tailed Student's t tests (B) or one-way ANOVA (A).

89



90

91 **Figure S5. M2 macrophage-enriched CHIL3/CHI3L1 functions as a downstream**
 92 **effector of the 5-ALA-CX3CR1 axis following HIR. Related to Figure 5.**

93 (A) Gating strategy for flow cytometry analysis of intrahepatic immune cells in

94 Figure 5A-B.

95 (B) Up: flow cytometry analysis of M1 (CD45⁺F4/80⁺CD86⁺) and M2

96 (CD45⁺F4/80⁺CD86⁻CD206⁺) macrophages in *WT* and *Cx3cr1* KO mouse livers at indicated

97 conditions; down: percentage of M1 (CD45⁺F4/80⁺CD86⁺) and M2

98 (CD45⁺F4/80⁺CD206⁺) macrophages in *WT* and *Cx3cr1* KO mouse livers at indicated
99 conditions (n = 6 for sham, n = 6 for HIR 6 h).

100 (C) Heatmap of expressed M1-enriched genes in *WT* and *Cx3cr1* KO mouse liver
101 samples at indicated conditions (n = 5). Red, high relative expression; blue, low
102 relative expression.

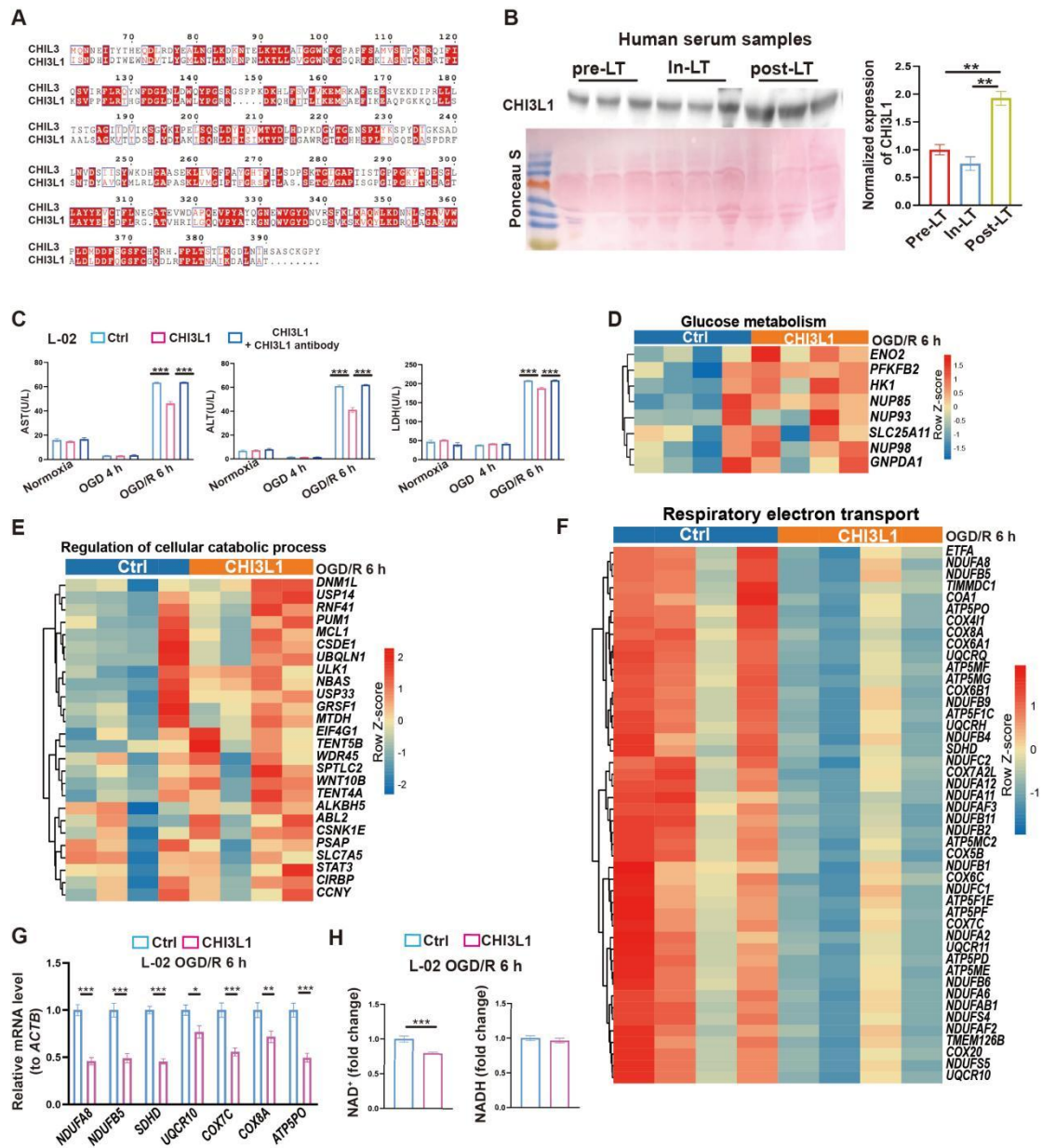
103 (D) Representative western blots of hepatic CHIL3 proteins in *WT* and *Cx3cr1* KO
104 mouse liver samples at indicated conditions. The CHIL3 signal intensity is normalized
105 to that of ACTB (n = 4 per group).

106 (E) Relative mRNA levels of *Chil3* normalized to that of *Actb* in mouse livers at
107 indicated conditions (n = 6 per group).

108 (F) Relative mRNA levels of *Chil3* normalized to that of *Actb* in mouse primary
109 hepatic macrophages at indicated conditions (n = 6 per group).

110 (G) Representative confocal images of CHIL3 (red), phalloidin (gray) and DAPI (blue)
111 in mouse liver sections at indicated conditions (scale bar = 10 μ m).

112 Results are presented as mean \pm SEM. **P* < 0.05, ***P* < 0.01, ****P* < 0.001 by
113 one-way ANOVA (B), (D), (E) and (F).



114

115 **Figure S6. CHIL3/CHI3L1 affects human hepatocytic metabolism following**

116 **OGD/R. Related to Figure 5 and 6.**

117 (A) Sequence homology analysis of human CHI3L1 and mouse CHIL3 proteins.

118 (B) Representative western blots of CHI3L1 proteins in patients' serum samples at

119 indicated conditions. The CHI3L1 signal intensity is normalized to the total proteins

120 stained with Ponceau S (n = 3 per group).

121 (C) AST, ALT and LDH levels in medium supernatant of L-02 cultures at indicated
122 conditions (n = 5).

123 (D) Heatmap of DEGs related to glucose metabolism (R-HSA-70326) in L-02
124 cultures at indicated conditions (n = 4 per group). Red, high relative expression; blue,
125 low relative expression.

126 (E) Heatmap of DEGs related to regulation of cellular catabolic process (GO:0031329)
127 in L-02 cultures at indicated conditions (n = 4 per group). Red, high relative
128 expression; blue, low relative expression.

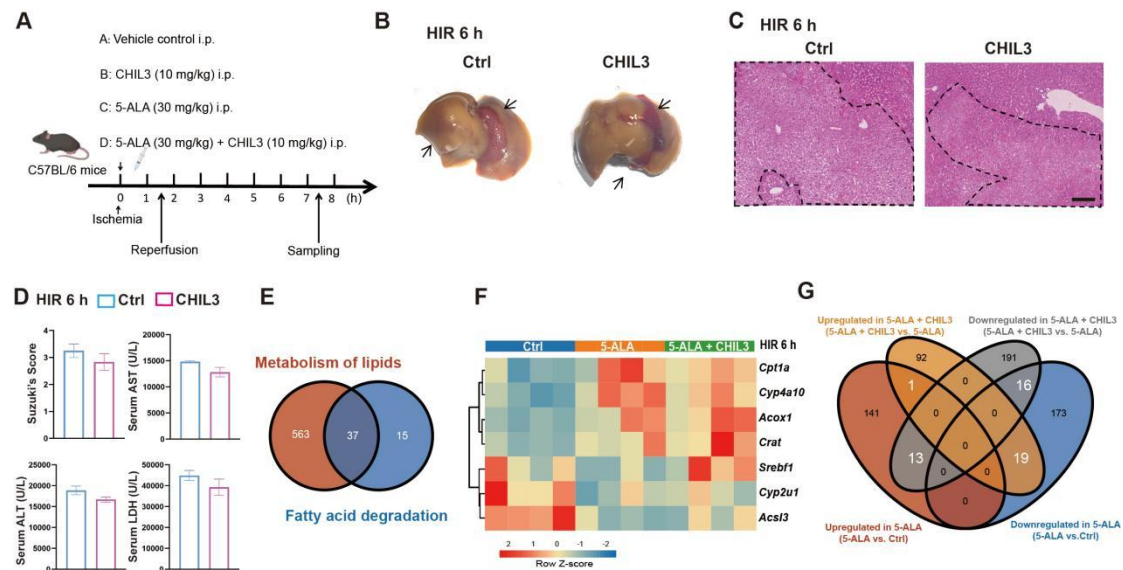
129 (F) Heatmap of DEGs related to respiratory electron transport (R-HSA-163200) in
130 L-02 cultures at indicated conditions (n = 4 per group). Red, high relative expression;
131 blue, low relative expression.

132 (G) Relative mRNA expression of selected genes related to the mitochondrial
133 respiratory electron transport (*NDUFA8*, *NDUFB5*, *SDHD*, *UQCRI0*, *COX7C*,
134 *COX8A* and *ATP5PO*) in L-02 cultures at indicated conditions (n = 12). The mRNA
135 level of each gene is normalized to that of *ACTB*.

136 (H) NAD⁺ and NADH levels (n = 9) in L-02 cells at indicated conditions.

137 Results are presented as mean ± SEM. **P* < 0.05, ***P* < 0.01, ****P* < 0.001 by
138 two-tailed Student's *t* tests (G) and (H) or one-way ANOVA (B) and (C).

139



140

141 **Figure S7. 5-ALA and/or CHIL3 treatments profoundly affect hepatic lipid**

142 **metabolism. Related to Figure 7.**

143 (A) Outline of the HIR experiments with mice subjected to indicated treatments.

144 (B) Gross appearance of mouse livers at indicated conditions (arrows denote areas of
 145 HIR injury).

146 (C) Representative H&E staining of mouse liver sections at indicated conditions,
 147 suggesting no overt difference between the control (ctrl) and CHIL3-treated group
 148 (areas of HIR injury are marked by broken lines; scale bar = 0.1 mm).

149 (D) Liver injury indicators Suzuki's score, and serum AST, ALT and LDH levels in
 150 mice with indicated conditions 6 h after HIR (n = 6 per group).

151 (E) Venn diagram indicating the number of overlapped genes in the metabolism of
 152 lipids (R-MMU-556833) (see Figure 3A) and fatty acid degradation (MMU00071)
 153 (see Figure 7A) pathways.

154 (F) Among the 37 overlapped genes from (E), heatmap of 7 genes differentially
 155 regulated by 5-ALA or a combined treatment of 5-ALA and CHIL3 6 h after HIR is

156 shown (n = 4 per group). Red, high relative expression; blue, low relative expression.
157 These may be important effector genes regulated by 5-ALA and CHIL3 to facilitate
158 liver lipid catabolism and energy production following HIR in mice. Also see Data
159 S2.

160 (G) Quadruple Venn diagram indicating the numbers of overlapped DEGs in
161 indicated comparisons. Also see Data S2.

162 Results are presented as mean \pm SEM. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ by
163 two-tailed Student's t tests (D).

164 **Table S1. Basic characteristics of liver transplantation donors and recipients.**

165 **Related to Figure 1 and Figure S6.**

	Age	Gender	Medical condition	Cold ischemia time * (min)	Time for post-operation liver biopsy (min)	Weight of liver
Donor 1	17	M	Trauma	431	67	22.1
Donor 2	59	M	Trauma	263	113	23.5
Donor 3	49	M	Trauma	357	74	21
Donor 4	27	F	Trauma	358	82	21.4
Donor 5	28	M	Trauma	381	95	23.7
Donor 6	27	M	Trauma	399	65	27.3
Donor 7	15	F	Trauma	407	132	22.5
Donor 8	55	M	Stroke	449	75	18.5
Donor 9	56	F	Encephalitis	370	79	26.6
Donor 10	32	M	Trauma	420	84	15.5
Donor 11	23	M	Trauma	500	83	26.3
Donor 12	30	M	Stroke	251	97	18.8
Donor 13	56	M	Stroke	570	102	33.2
Donor 14	50	M	Stroke	360	58	18.6
Donor 15	56	M	Stroke	340	68	20.7
Donor 16	68	M	-	230	74	22.5
Donor 17	54	F	Stroke	397	89	31
Donor 18	28	M	Stroke	330	97	22.6
Donor 19	55	M	-	429	99	15.6
Donor 20	58	M	Stroke	380	88	20.5

166 * Surgery-related ischemia time was typically below 30 min.

167

	Age	Gender	Medical condition	Liver from
Recipient 1	47	M	Liver cirrhosis	Donor 4
Recipient 2	52	M	Liver cirrhosis	Donor 10
Recipient 3	51	M	Liver cirrhosis	Donor 11

168

169 **Table S2. Gene primers used for quantitative RT-PCR and genotyping.**

170 **Primers for quantitative RT-PCR related to Figure 1.**

Gene	Forward Primer	Reverse Primer
<i>ALAS1</i>	CGCCGCTGCCCATTTCTTAT	TCTGTTGGACCTTGGCCTTAG
<i>ALAD</i>	GCTACTTCCACCCACTACTTCG	TCAGGAACATCCGTGACAAAG
<i>HMOX1</i>	AAGACTGCGTTCCTGCTCAAC	AAAGCCCTACAGCAACTGTCG
<i>UROD</i>	ATGGAAGCGAATGGGTTGGG	GGGAGTGTAGTCTGTTTCCTCT
<i>UROS</i>	GCCAAGTCAGTGTATGTGGTT	GCAATCCCTTTGTCCTTGAGC
<i>PPOX</i>	CTGGATTCGCTCCGTTTCGAG	CCCACGTAGAGGAACCTGT

171

172 **Primers for quantitative RT-PCR related to Figure 4.**

Gene	Forward Primer	Reverse Primer
<i>Ccr1</i>	GCCCTCATTGCCCTACAA	CGGCTTTGACCTTCTTCTCA
<i>Ccr2</i>	TGTGATTGACAAGCACTTAGA CC	TGGAGAGATACCTTCGGA ACT T
<i>Ccr5</i>	ATGGATTTTCAAGGGTCAGTT CC	CTGAGCCGCAATTTGTTTCAC
<i>Ccr7</i>	CATGGACCCAGGTGTGCTTC	TCAGTATCACCAGCCCGTTG
<i>Ccr8</i>	TGTTTGGGACTGCGATGTGT	TGATGGCATAGACAGCGTGG
<i>Cx3cr1</i>	CAAGCTCACGACTGCCTTCT	TGTCCGGTTGTTTCATGGAGT
<i>Actb</i>	AGCCATGTACGTAGCCATCC	CTCTCAGCTGTGGTGGTGAA

173

174 **Primers for quantitative RT-PCR related to Figure 6.**

Gene	Forward Primer	Reverse Primer
<i>SERPINE1</i>	ACCGCAACGTGGTTTTCTCA	TTGAATCCCATAGCTGCTTG AAT
<i>EGFR</i>	AGGCACGAGTAACAAGCTCA C	ATGAGGACATAACCAGCCAC C
<i>SLC2A1</i>	GGCCAAGAGTGTGCTAAAGA A	ACAGCGTTGATGCCAGACAG
<i>ENO1</i>	AAAGCTGGTGCCGTTGAGAA	GGTTGTGGTAAACCTCTGCT C
<i>HK1</i>	GCTCTCCGATGAAACTCTCA TAG	GGACCTTACGAATGTTGGCA A
<i>PPARA</i>	ATGGTGGACACGGAAAGCC	CGATGGATTGCGAAATCTCT TGG
<i>ACO1</i>	ACTCGCAGCCAGCGTTATG	AGGGTCAGCGATGCCAAAC

175

176 **Primers for quantitative RT-PCR related to Figure S1C.**

Gene	Forward Primer	Reverse Primer
<i>Hmox1</i>	AGGTACACATCCAAGCCGAGA	CATCACCAGCTTAAAGCCTTCT

177

178 **Primers for quantitative RT-PCR related to Figure S3 and S4.**

Gene	Forward Primer	Reverse Primer
------	----------------	----------------

<i>Inos</i>	CCTAGTCAACTGCAAGAGAA T	TTTCAGGTCACTTTGGTAGG
<i>Il1b</i>	CCACCTTTTGACAGTGATGA AG	GAGATTTGAAGCTGGATGCT C
<i>Cd206</i>	GGTGGAAGAAGAAGTAGCC T	GAAGGGTCAGTCTGTGTTTG
<i>Arg1</i>	CTCCAAGCCAAAGTCCTTAG AG	AGGAGCTGTCATTAGGGACAT C
<i>Il10</i>	TGTCAAATTCATTCATGGCC T	ATCGATTTCTCCCCTGTGAA
<i>Il6</i>	CCGGAGAGGAGACTTCACA GA	TCCACGATTTCCAGAGAAC
<i>Rela</i>	AGGCTTCTGGGCCTTATGTG	TGCTTCTCTCGCCAGGAATAC
<i>Tnfa</i>	CCCTCACACTCAGATCATCT TCT	GCTACGACGTGGGCTACAG

179

180 **Primers for quantitative RT-PCR related to Figure S6G.**

Gene	Forward Primer	Reverse Primer
<i>NDUFA8</i>	CCCAACAAGGAGTTTATGC TCT	CACAGTGACGTTTTATCTGCCT
<i>NDUFB5</i>	AGCTGGAAGTGCGAAAATT GA	ATACCAGGGTCCATCTCCTCT
<i>ATP5PO</i>	ATTGAAGGTCGCTATGCCA CA	GCTTTTCACTTTAATGGAACGC T

<i>COX8A</i>	GCCAAGATCCATTCGTTGCC	CTCTGGCCTCCTGTAGGTCT
<i>COX7C</i>	GGTCCGTAGGAGCCACTAT GA	GTGTCTTACTACAAGGAAGGG TG
<i>UQCR10</i>	ATCGTGGGCGTCATGTTCTT C	ATGTGGTCGTAGATAGCGTCC
<i>SDHD</i>	ATTTCTTCAGGACCGACCTA TCC	CAGCCTTGGAGCCAGAATG
<i>ACTB</i>	GTGACGTGGACATCCGCAA AGA	TGGAAGGTGGACAGCGAGGC

181

182 **Primers for Genotyping related to Figure 4.**

Gene	Forward Primer	Reverse Primer
<i>Cx3cr1</i> wildtype	GTCTTCACGTTCCGGTCTGGT	CCCAGACACTCGTTGTCCTT
<i>Cx3cr1</i> mutant	CTCCCCCTGAACCTGAAAC	CCCAGACACTCGTTGTCCTT

183 **Table S3. Primary antibodies**

Antibodies	Source	Identifier
Rabbit anti CHIL3	Abcam	Cat# ab192029
Rabbit anti CHI3L1	SAB	Cat# 35680
Rat anti F4/80 (for IF-Frozen)	Abcam	Cat# ab6640
Rabbit anti F4/80 (for IHC-P, IF-P)	CST	Cat# 70076
Rabbit anti CX3CR1	Abcam	Cat# ab8021

Rabbit anti ACTB	CST	Cat# 4970
Rabbit anti CCR1	ABclonal	Cat# A18341
Rabbit anti CCR5	Abcam	Cat# ab7346
Rabbit anti CD206	Abcam	Cat# ab64693
Mouse anti ALAD	Santa Cruz	Cat# sc-271585
Mouse anti ALAS1	Santa Cruz	Cat# sc-137093
Mouse anti p65 NF- κ B	Santa Cruz	Cat# sc-8008
Rabbit anti TGF beta 1	ABclonal	Cat# A2124
Rabbit anti Ly-6G	Abcam	Cat# ab25377
Rat anti CD11b	Abcam	Cat# ab128797
PerCP/Cyanine5.5 anti-mouse CD45	Biolegend	Cat# 103131
Brilliant violet 510 anti-mouse/human CD11b	Biolegend	Cat# 101263
APC anti-mouse F4/80	Biolegend	Cat# 123116
Alexa fluor anti-mouse Ly-6C	Biolegend	Cat# 128023
PE anti-mouse CD206	Biolegend	Cat# 141706
Brilliant violet 605 anti-mouse CD86	Biolegend	Cat# 105037

185 **Table S4. Other reagents**

Reagents	Source	Identifier
Goat anti-Mouse IgG (H+L) Secondary Antibody, HRP conjugate	Invitrogen	Cat# 31430
Goat anti-Rabbit IgG (H+L) Secondary Antibody, HRP conjugate	Invitrogen	Cat# 31460
Alexa Fluor 488 goat anti-rat IgG (H+L)	Invitrogen	Cat# A-11006
Alexa Fluor 594 goat anti-rat IgG (H+L)	Invitrogen	Cat# A-11007
Alexa Fluor 488 goat anti-mouse IgG (H+L)	Invitrogen	Cat# A-11001
Alexa Fluor 594 goat anti-mouse IgG (H+L)	Invitrogen	Cat# A-11005
Alexa Fluor 488 goat anti-rabbit IgG (H+L)	Invitrogen	Cat# A-11008
BODIPY	Invitrogen	Cat# D3922
MitoNeoD	MedKoo Biosciences	Cat# 563761
Phalloidine 633	Thermo Fisher Scientific	Cat# A22284
TMRE	MCE	Cat# HY-D0985A
Hoechst 33342	Invitrogen	Cat# H3570
DAPI	Invitrogen	Cat# D1306
Tissue-Tek O.C.T Compound	Sakura	Cat# 4583
Taq Pro Universal SYBR qPCR Master Mix	Vazyme	Cat# Q712
HiScript III RT SuperMix for qPCR (+gDNA	Vazyme	Cat# R323

wiper)		
Brewer's medium	Solarbio	Cat# LA4590
RPMI 1640	Gibco	Cat# C11875500BT
DMEM	Gibco	Cat# C11995500BT
Fetal Bovine Serum	PAN	Cat# P30-3302
M-PER Mammalian Protein Extraction Reagent	Invitrogen	Cat# 78501
T-PER Tissue Protein Extraction Reagent	Invitrogen	Cat# 78510
NuPAGE Sample Reducing Agent (10X)	Invitrogen	Cat# NP0004
NuPAGE LDS Sample Buffer (4X)	Invitrogen	Cat# NP0008
TRIzol	Invitrogen	Cat# 15596026
Mouse Mononuclear Cells Separation Medium	Dakewe	Cat# 7211011
Corn oil	Macklin	Cat# C805618
DMSO	Sigma-Aldrich	Cat# D2650
Collagenase IV	Sigma-Aldrich	Cat# C5138

187 **Table S5. Chemicals, peptides, and recombinant proteins**

Chemicals, peptides, and recombinant proteins	Source	Identifier
5-Aminolevulinate	Macklin	Cat# A800543
CHIL3	MCE	Cat# HY-P7845
CHI3L1	MCE	Cat# HY-P70030
IL-4	Peptotech	Cat# 214-14
LPS from <i>E. coli</i> O111:B4	Sigma-Aldrich	Cat# L2630
Rotenone	Sigma-Aldrich	Cat# R8875
Decylubiquinone	Sigma-Aldrich	Cat# D7911
NaN ₃	Sigma-Aldrich	Cat# S2002
Cytochrome c	Sigma-Aldrich	Cat# C2867
Antimycin A	Sigma-Aldrich	Cat# A8674
BAY-11-7082	MCE	Cat# HY-13453
Betulinic acid	MCE	Cat# HY-10529
T0070907	Selleck	Cat# S2871
Fenofibric acid	Macklin	Cat# 42017-89-0

188

189 **Table S6. Critical commercial assays**

Critical commercial assays	Source	Identifier
Dako REAL EnVision Detection System, Peroxidase/DAB+ Rabbit/Mouse	Dako	Cat# K5007
TrueView Autofluorescence Quenching kit	Vector	Cat# SP-8500
ECL Chemiluminescent HRP Substrate	Advansta	Cat# K-12045
ECL Ultra Western HRP Substrate	Merck Millipore	Cat# CS222618
Seahorse XF Real-Time ATP Rate Assay Kit	Seahorse	Cat# 103592-100
Mouse YM1/Chitinase 3 like 3 ELISA Kit	RayBio	Cat# ELM-YM1
Mouse IL-1 β ELISA Kit	Neobioscience	Cat# EMC001b
Mouse IL-6 ELISA Kit	Neobioscience	Cat# EMC004
Mouse IL-10 ELISA Kit	Neobioscience	Cat# EMC005
Mouse TNF- α ELISA Kit	Neobioscience	Cat# EMC102a
ATP assay kit	Nanjing Jiancheng Bioengineering Institute	Cat# A095-1-1
Lactate assay kit	Solarbio	Cat# BC2230
NADP/NADPH Quantitation Colorimetric Kit	biovison	Cat# K347-100
NAD ⁺ /NADH Colorimetric Assay Kit	biovison	Cat# K958-400
Mitochondrial Complex IV activity assay kit	Acmecc	Cat# BC0940
Mitochondrial Complex V activity assay kit	Solarbio	Cat# BC1445
CCK-8 Cell Counting Kit	Vazyme	Cat# A311

In Situ Cell Death Detection Kit, Fluorescein	Roche	Cat# 11684795910
NEBNext® Ultra™ RNA Library Prep Kit	NEB	Cat# E7775

190

191 **Table S7. Experimental models**

Experimental models	Source	Identifier
Human: L-02	ATCC	CRL-2524
Mouse: B6.129P2(Cg)-Cx3cr1 ^{tm1Litt} /J	Jackson lab	005582
Mouse: C57BL6/J	Zhuhai BesTest Bio-Tech Co.,Ltd	N/A

192

193 **Table S8. Software and algorithms**

Software and algorithms	Source	Identifier
R v4.0.2	The R Foundation	https://www.r-project.org
Hisat2 v2.0.5	Kim et al. [1]	http://daehwankimlab.github.io/hisat2/
featureCounts package v2.0.1	Liao et al. [2]	https://subread.sourceforge.net/featureCounts.html
DESeq2 package 1.26.0	Love et al. [3]	https://bioconductor.org/packages/release/bioc/html/DESeq2

		eq2.html
Graphpad Prism 8.0	Graphpad	https://www.graphpad.com/
Zen 2.6	Zeiss	https://www.zeiss.com/microscopy/en/products/software/zeiss-zen.html
TissueFAXS SL Viewer 7.0.6245	Tissuegnostics	https://tissuegnostics.com/products/scanning-and-viewing-software/tissuefaxes-viewer
Oxymax/CLAMS	Columbus	https://www.colinst.com/downloads/?p=0
ImageJ 1.53	National Institutes of Health	https://imagej.nih.gov/ij/
CytExpert 2.4	Beckman	https://www.beckman.com/flow-cytometry/research-flow-cytometers/cytoflex/software

194

195 **Supplemental References**

- 196 1. Kim D, Paggi JM, Park C, Bennett C, Salzberg SL. Graph-based genome alignment and
197 genotyping with HISAT2 and HISAT-genotype. *Nature Biotechnology*. 2019; 37: 907-15.
- 198 2. Liao Y, Smyth GK, Shi W. featureCounts: an efficient general purpose program for assigning
199 sequence reads to genomic features. *Bioinformatics*. 2013; 30: 923-30.
- 200 3. Love MI, Huber W, Anders S. Moderated estimation of fold change and dispersion for
201 RNA-seq data with DESeq2. *Genome Biology*. 2014; 15.

202