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Supplemental Material

Role of Hepatocyte- and Macrophage-Specific PPARγ in Hepatotoxicity Induced by Diethylhexyl Phthalate in Mice

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Additional File- Excel Document

Table S1 Key reagents and materials

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Antibodies		
PE anti-human CCR7 (clone#G043H7, FACS: 2 μl /10^6 cells)	Biolegend	Cat#353204, RRID: AB_10913813
Alexa Fluor® 647 anti-human CCR7 (clone#G043H7, FACS: 2 μl /10^6 cells)	Biolegend	Cat#353218; RRID: AB_10917385
PE anti-human CD209 (clone#9E9A8, FACS: 2 μl /10^6 cells)	Biolegend	Cat#330106; RRID:AB_1134052
FITC anti-human CD209 (clone#9E9A8, FACS: 2 μl /10^6 cells)	Biolegend	Cat#330104; RRID:AB_1134048
PE anti-human CD36 antibody(clone#AC106, FACS: 2 μl /10^6 cells)	Miltenyi	Cat#130-095-472; RRID:AB_10827705
PE anti-mouse CD206 (clone#C068C2, FACS: 0.5 μg /10^6 cells)	Biolegend	Cat#141706; RRID:AB_10895754
APC anti-mouse CD206 (clone#C068C2, FACS: 0.5 μg /10^6 cells)	Biolegend	Cat#141708; RRID:AB_10900231
FITC anti-mouse CD206 (clone#C068C2, FACS: 0.5 μg /10^6 cells)	Biolegend	Cat#141704; RRID:AB_10901166
Alexa Fluor® 647 anti-mouse CD69 (clone#H1.2F3, FACS: 0.25 μg /10^6 cells)	Biolegend	Cat#104518; RRID:AB_492847
APC anti-mouse CD36 (clone#HM36, FACS: 0.25 μg /10^6 cells)	Biolegend	Cat#102612; RRID:AB_2072639
PerCP/Cyanine5.5 anti-CD11b (clone#M1/70, FACS: 0.25 μg /10^6 cells)	Biolegend	Cat#123126; RRID:AB_893483
PE anti-mouse F4/80(Clone#BM8, FACS: 0.5 μg /10^6 cells)	Biolegend	Cat#123110; RRID:AB_893486
PerCP anti-mouse F4/80(Clone#BM8, FACS: 0.5 μg /10^6 cells)	Biolegend	Cat#123126; RRID:AB_893483
PerCP/Cyanine5.5 anti-mouse CD45 (clone#30-F11, FACS: 0.25 μg /10^6 cells)	Biolegend	Cat#103132; RRID:AB_893340
FITC anti-mouse CD45 (clone#30-F11, FACS: 0.25 μg /10^6 cells)	Biolegend	Cat#103108; RRID:AB_312973
APC Anti-mouse CD45 (clone#30-F11, FACS: 0.25 μg /10^6 cells)	Biolegend	Cat#103112; RRID:AB_312977
PE anti-mouse CCR2 (clone# SA203G11, FACS: 0.5 μg /10^6 cells)	Biolegend	Cat#150610; RRID:AB_2616982
Alexa Fluor® 647 anti-mouse CCR2 (clone# SA203G11, FACS: 0.5 μg /10^6 cells)	Biolegend	Cat#150604; RRID:AB_2566140
APC anti-mouse LY6C (clone#HK1.4, FACS: 0.1 μg /10^6 cells)	Biolegend	Cat# 128016; RRID:AB_1732076
PPARγ rabbit mAb (clone# C26H12, IHC:1/200)	Cell Signaling Technology	Cat#2435S; RRID:AB_2166051

Ki-67 rabbit mAb (clone# D3B5, IHC:1/200)	Cell Signaling Technology	Cat#12202; RRID:AB_2620142
F4/80 rabbit mAb (clone# D4C8V, IHC:1/200)	Cell Signaling Technology	Cat#30325; RRID:AB_2798990
PPAR alpha polyclonal antibody(IHC:1/200)	Invitrogen	Cat#PA1-822A; RRID:AB_2165595
Mouse CLEC4F/CLECSF13 antibody(IHC:1/200)	R&D systems	Cat#AF2784; RRID:AB_2081339
Mouse IL-1ra/IL-1F3 antibody (clone# 962802, IHC: 10 μg/ml)	R&D systems	Cat#MAB4802; N/A
COX7A2L Rabbit Polyclonal antibody(IHC: 1/100)	Proteintech	Cat#11416-1-AP; RRID:AB_2245402
Rabbit anti-rat IgG H&L, HRP (IHC: 1/1000)	Abcam	Cat#ab6734; RRID:AB_955450
Donkey anti-goat IgG H&L, HRP (IHC:1/1000)	Santa Cruz	Cat#SC-2033; RRID:AB_631729
Chemicals, Peptides, and Recombinant Proteins		
Recombinant Human IL-4	Peprotech	Cat#200-04
Recombinant Human IL-13	Peprotech	Cat#AF-200-13
Recombinant Human IFNγ	Peprotech	Cat#300-02
Recombinant Murine M-CSF	Peprotech	Cat#315-02
Recombinant Murine IL-4	Peprotech	Cat#214-14
Recombinant Murine IL-13	Peprotech	Cat#210-13
Recombinant Murine IFNγ	Peprotech	Cat#315-05
Recombinant human IL1RA	R&D systems	Cat#280-RA-050
Human PPARγ protein	Sino Biological	Cat#12019-H20B
Human PPARα protein	Abnova	Cat#H00005465-P01
Human PPARδ protein	Abnova	Cat#H00005467-P01
Lipopolysaccharides (LPS)	Sigma Aldrich	Cat#L6529
Phorbol 12-myristate 13-acetate (PMA)	Sigma Aldrich	Cat#P8139
DEHP	Sigma Aldrich	Cat# 67261
MEHP	MedChemExpress	Cat# HY-W018392
WY14643	R&D systems	Cat#1312
Rosiglitazone	Cayman	Cat#71740
T0070907	R&D systems	Cat#2301
GW9662	Cayman	Cat#70785
GW6471	MedChemExpress	Cat# HY-15372
Critical Commercial Assays		
Foxp3 / Transcription Factor Staining Buffer Set	Invitrogen	Cat#00-5523-00
LEGENDplex Human Macrophage/Microglia Panel	Biolegend	Cat#740502
LEGENDplex Mouse Macrophage/Microglia Panel	Biolegend	Cat#740845
RNeasy Mini Kit	QIAGEN	Cat#74104
Opal multiplex IHC research kit	Perkin Elmer	Cat# NEL810001KT

DAB substrate kit	Cell Signaling Technology	Cat#8095S
Deposited Data		
Raw and analyzed data	This paper; and Mendeley Data	http://dx.doi.org/10.17632/zd6pt6hb7y.1
RNA-sequencing data	This paper	GEO: GSE159120
RNA-sequencing data	This paper	GEO: GSE160004
RNA-sequencing data	This paper	GEO: GSE160373;
RNA-sequencing data	This paper	GEO: GSE160826
Experimental Models: Cell Lines		
THP-1	American Type Culture Collection	Cat#TIB-202; RRID:CVCL_0006
THP-1 with PPRE-eGFP	This paper	N/A
HepG2	Cell Bank of Type Culture Collection Committee of the Chinese Academy of Sciences	Cat#SCSP-510; N/A
Experimental Models: Organisms/Strains		
Mouse: C57BL/6	In house breeding	N/A
Mouse: PPARγ^{loxP}:B6.129-*Pparg*^{tm2Rev}/J	Jackson Laboratory	Cat# JAX:004584, RRID:IMSR_JAX:004584
Mouse: LysM^{Cre}: B6.129P2-*Lyz2*$^{tm1(cre)Ifo}$/J	Jackson Laboratory	Cat# JAX:004781, RRID:IMSR_JAX:004781
Mouse: Alb^{Cre}: B6.Cg-*Speer6-ps1*$^{Tg(Alb-cre)21Mgn}$/J	Jackson Laboratory	Cat# JAX:003574, RRID:IMSR_JAX:003574
Recombinant DNA		
Plasmid: PPRE-H2B-eGFP	Addgene	Cat#84393; RRID:Addgene_84393
Software and Algorithms		
GraphPad prism (v 6.01)	GraphPad Software	https://www.graphpad.com/
ImageXpress(v6.0)	Molecular Device	https://www.moleculardevices.com
Other		
Human TruStain FcX	Biolegend	Cat#422302
TruStain FcX (anti-mouse)	Biolegend	Cat#101320
Fetal Bovine Serum (FBS)	Gibco	Cat#10099141C
Fixation and Permeabilization Solution	BD Bioscience	Cat#554722
FluoroBrite™ DMEM	Gibco	Cat#A1896702

Hoechst 33342	Solarbio	Cat#C0031
Perm/Wash buffer	BD Bioscience	Cat#554723
RPMI 1640 (ATCC modification)	Gibco	Cat#A1049101
2-mercaptoethanol	Sigma Aldrich	Cat#M3148
BODIPY 493/503	Invitrogen	Cat#D3922
HCS LipidTOX™ Red Neutral Lipid Stain, for cellular imaging	Invitrogen	Cat#34476
TMRE	Abcam	Cat# ab113852
MitoSOX™ Red Mitochondrial Superoxide Indicator	Invitrogen	Cat# M36008
CellROX deep red	Invitrogen	Cat#C10491

Table S2 Liver weight and liver index in DEHP treated mice [mean ± SD; n=10/group].

Dose group	**0 mg/kg BW**	**625 mg/kg BW**	**1250 mg/kg BW**	**2500 mg/kg BW**
Liver weight(g)	1.08±0.13	1.29±0.05***	1.28±0.11***	1.49±0.08***
Liver index(%BW)	4.68±0.37	5.38±0.30***	5.35±0.39***	6.50±0.29***

Note: Correspond to Figure 1A. BW, body weight; DEHP, di(2-Ethylhexyl) phthalate; SD, standard deviation. *p<0.05, **p<0.01, ***p<0.001, relative to vehicle control [analysis of variance (one-way ANOVA) with post hoc multiple comparison correction using Dunnett's multiple comparisons test].

Table S3 Concentration of MEHP in plasma and liver of DEHP treated mice [mean ± SD (n)].

Dose group	**0 mg/kg BW**	**625 mg/kg BW**	**1250 mg/kg BW**	**2500 mg/kg BW**
For Figure 1B:	0.40±0.44	16.36±5.71*	25.34±4.54**	53.26±18.61***
Plasma(ng/ml)	(6)	(6)	(6)	(6)
For Figure 1C:	24.45±12.69	273.64±32.97*	335.77±80.03*	659.85±277.48***
Liver(ng/g tissue)	(5)	(5)	(5)	(5)

Note: Correspond to Figure 1B and 1C. BW, body weight; DEHP, di(2-Ethylhexyl) phthalate; SD, standard deviation; MEHP, mono-2-ethylhexyl phthalate. *p<0.05, **p<0.01, ***p<0.001, relative to vehicle control [analysis of variance (one-way ANOVA) with post hoc multiple comparison correction using Dunnett's multiple comparisons test].

Table S4 Clinical chemistry panel of DEHP treated mice [mean ± SD; n=5/group]

Dose group	**0 mg/kg BW**	**625 mg/kg BW**	**1250 mg/kg BW**	**2500 mg/kg BW**
TG(mM)	0.74±0.11	0.58±0.07**	0.53±0.04***	0.55±0.03**
CHO(mM)	1.55±0.14	1.66±0.08	1.86±0.07**	2.12±0.18***
LDLC(mM)	0.25±0.04	0.26±0.02	0.27±0.04	0.32±0.03**
HDLC(mM)	1.04±0.13	1.15±0.05	1.19±0.10	1.37±0.10***
ALP(U/L)	73.96±3.05	79.60±7.16	90.00±7.04**	106.40±5.27***

Note: Correspond to Figure 1D. ALP, alkaline phosphatase; BW, body weight; CHO, cholesterol; DEHP, di(2-Ethylhexyl) phthalate; HDLC, high-density lipoprotein cholesterol; LDLC, low-density lipoprotein cholesterol; SD, standard deviation; TG, triglycerides; U/L, units per liter. *p<0.05, **p<0.01, ***p<0.001, relative to vehicle control [analysis of variance (one-way ANOVA) with post hoc multiple comparison correction using Dunnett's multiple comparisons test].

Table S5 Concentration of hepatic TG in DEHP treated mice [mean ± SD; n=5/group].

Dose group	**0 mg/kg BW**	**625 mg/kg BW**	**1250 mg/kg BW**	**2500 mg/kg BW**
Liver(μg/mg tissue)	1.02±0.25	2.48±0.57**	4.59±1.04***	6.25±0.55***

Note: Correspond to Figure 1E. BW, body weight; DEHP, di(2-Ethylhexyl) phthalate; SD, standard deviation; TG, triglycerides. *p<0.05, **p<0.01, ***p<0.001, relative to vehicle control [analysis of variance (one-way ANOVA) with post hoc multiple comparison correction using Dunnett's multiple comparisons test].

Table S6 Hepatic pathological severity and oil red staining evaluation in DEHP treated mice [evaluating scores; mean ± SD; n=6/group].

Dose group	**0 mg/kg BW**	**625 mg/kg BW**	**1250 mg/kg BW**	**2500 mg/kg BW**
Hepatic pathological severity	1.33±0.52	6.00±2.45**	11.17±3.37***	14.17±2.99***
Oil red staining intensity	1.17±0.41	3.33±1.51	10.00±3.52***	12.17±3.37***

Note: Correspond to Figure 1F. BW, body weight; DEHP, di(2-Ethylhexyl) phthalate; SD, standard deviation. *p<0.05, **p<0.01, ***p<0.001, relative to vehicle control [analysis of variance (one-way ANOVA) with post hoc multiple comparison correction using Dunnett's multiple comparisons test].

Table S7 Fatty acid uptake and lipid accumulation evaluation in MEHP treated HepG2 cells [Mean stain area (μm^2) (% of control); mean ± SD; n=4/treatment].

Dose(log10, μM)	BODIPY FL C12 uptake	LD lipid accumulation
2.30	386.06±20.77***	/
2.00	385.18±68.99***	/
1.41	309.85±72.84***	/
1.13	265.58±67.09***	/
0.86	202.41±21.33*	/
0.62	166.26±29.19	/
0.41	151.71±15.03	/
0.00(control)	100.00±0.00	/
2.30	/	145.91±12.61***
2.00	/	155.81±5.08***
1.71	/	135.88±2.01***
1.41	/	134.99±10.78***
1.13	/	118.89±9.69*
0.62	/	104.89±5.42
0.41	/	103.87±9.74
0.00(control)	/	100.00±0.00

Note: Correspond to Figure 1G. BODIPY FL C16, fluorescence probe for C16 fatty acids; LD, lipid droplet; MEHP, mono-2-ethylhexyl phthalate; SD, standard deviation. *p<0.05, **p<0.01, ***p<0.001, relative to vehicle control [analysis of variance (one-way ANOVA) with post hoc multiple comparison correction using Dunnett's multiple comparisons test].

Table S8 Data for Figure 2A: Binding affinity analysis of PPARα [Resonance units (RU); n=2006-2146; provided as Excel Table S8].

Table S9 Data for Figure 2A: Binding affinity analysis of PPARγ [Resonance units (RU); n=1583-2131; provided as Excel Table S9].

Table S10 PPRE and CD36 response in PPRE-THP-1 cells derived macrophages [positive cells (%); mean±SD; n=6 sites/treatment].

Treatment	CT(DMSO)	WY	RGZ	T0070907	DEHP	MEHP
PPRE	22.84±4.63	29.54±4.64*	37.01±4.59***	24.21±2.22	28.83±1.67*	29.45±3.28*
CD36	35.11±4.02	47.14±6.56*	62.91±3.34***	29.48±3.07*	46.92±3.87*	52.04±6.81**

Note: Correspond to Figure 2C. CT, vehicle control; DMSO, dimethyl sulfoxide; DEHP, di(2-Ethylhexyl) phthalate; MEHP, mono-2-ethylhexyl phthalate; WY, WY14643, PPARα agonist; RGZ, rosiglitazone, PPARγ agonist; T0070907, PPARγ antagonist; SD, standard deviation. *p<0.05, **p<0.01, ***p<0.001, relative to vehicle control [analysis of variance (one-way ANOVA) with post hoc multiple comparison correction using Dunnett's multiple comparisons test].

Table S11 Dose response curves of PPRE in PPRE-THP-1 cells derived macrophages [mean stain area (μm^2); mean; n=3/treatment]**.**

Concentration(log10, μM)	WY	RGZ	GW6471	GW9662	T0070907
2.30	126.34	162.38	/	/	/
2.00	135.06	162.51	/	/	/
1.70	112.00	162.51	/	/	/
1.40	88.56	155.70	/	/	/
1.10	73.14	145.73	/	/	/
0.80	75.43	143.78	/	/	/
0.49	82.50	131.59	/	/	/
0.19	68.15	120.50	/	/	/
-6.00	73.26	73.26	/	/	/
1.30	/	/	58.37	83.08	44.42
1.00	/	/	67.38	86.19	48.07
0.70	/	/	66.57	82.34	44.93
0.40	/	/	74.31	93.06	43.01
0.10	/	/	74.07	94.15	48.01
-0.20	/	/	73.38	82.57	54.98
-0.51	/	/	62.74	75.32	58.90
-0.81	/	/	73.26	73.26	73.26

Note: Correspond to Figure 2D. WY, WY14643, PPARα agonist; GW6471, PPARα antagonist; GW9662, PPARγ antagonist; RGZ, rosiglitazone, PPARγ agonist; T0070907, PPARγ antagonist and inverse agonist.

Table S12 Dose response curve of CD36 in PPRE-THP-1 cells derived macrophages [mean stain area (μm^2); mean, n=3/treatment)].

Concentration(log10, μM)	WY	RGZ	GW6471	GW9662	T0070907
2.30	248.23	274.00	/	/	/
2.00	247.48	274.90	/	/	/
1.70	204.21	272.40	/	/	/
1.40	155.63	267.38	/	/	/
1.10	127.37	250.40	/	/	/
0.80	131.57	239.42	/	/	/
0.49	136.57	220.35	/	/	/
0.19	116.47	239.65	/	/	/
-1.20	118.64	118.64	118.64	118.64	118.64
1.30	/	/	91.82	142.00	32.87
1.00	/	/	104.29	142.11	38.05
0.70	/	/	106.56	144.74	49.87
0.40	/	/	111.02	146.70	44.93
0.10	/	/	120.55	156.97	44.53
-0.20	/	/	129.32	159.01	53.98
-0.51	/	/	123.97	140.34	61.82
-0.81	/	/	114.27	130.74	56.55

Note: Correspond to Figure 2D. WY, WY14643, PPARα agonist; GW6471, PPARα antagonist; GW9662, PPARγ antagonist; RGZ, rosiglitazone, PPARγ agonist; T0070907, PPARγ antagonist and inverse agonist.

Table S13 Dose response curve of PPRE and CD36 in MEHP treated macrophages with/without PPARα/γ antagonists [mean stain area (μm^2); mean, n=3/treatment]**.**

Concentration	MEHP		M+GW6471		M+GW9662		M+T0070907	
(log10, μM)	PPRE	CD36	PPRE	CD36	PPRE	CD36	PPRE	CD36
2.30	135.76	274.05	83.60	198.29	101.69	208.05	72.75	156.07
2.00	131.30	251.43	65.56	153.60	113.41	200.50	87.55	155.45
1.70	117.13	206.65	61.20	122.91	113.01	208.83	79.08	125.57
1.40	101.23	182.55	51.40	98.85	91.39	172.65	69.94	94.16
1.10	91.51	152.13	58.30	105.67	92.26	173.16	45.27	58.25
0.80	85.18	143.89	49.34	103.64	93.83	151.63	51.89	56.31
0.49	80.87	153.89	53.96	103.54	82.93	145.05	46.54	44.71
0.19	72.38	120.15	50.40	96.44	77.36	138.10	38.66	41.72
2.30	135.76	274.05	83.60	198.29	101.69	208.05	72.75	156.07
2.00	131.30	251.43	65.56	153.60	113.41	200.50	87.55	155.45
1.70	117.13	206.65	61.20	122.91	113.01	208.83	79.08	125.57
1.40	101.23	182.55	51.40	98.85	91.39	172.65	69.94	94.16
1.10	91.51	152.13	58.30	105.67	92.26	173.16	45.27	58.25
0.80	85.18	143.89	49.34	103.64	93.83	151.63	51.89	56.31
0.49	80.87	153.89	53.96	103.54	82.93	145.05	46.54	44.71
0.19	72.38	120.15	50.40	96.44	77.36	138.10	38.66	41.72

Note: Correspond to Figure 2E. GW6471, PPARα antagonist; GW9662, PPARγ antagonist; M, MEHP, mono-2-ethylhexyl phthalate; T0070907, PPARγ antagonist and inverse agonist.

Table S14 Liver weight and liver index in WT and Hep-KO mice [mean ± SD (n)]

	Treatment	**CMC**	**DEHP**
Liver weight(g)	WT	1.24±0.13 (7)	1.65±0.15 (7)**
	Hep-KO	1.16±0.17 (5)	1.60±0.08 (5)**
Liver index(%BW)	WT	4.69±0.48 (7)	6.34±0.37 (7)***
	Hep-KO	4.45±0.52 (5)	6.23±0.14 (5)***

Note: Correspond to Figure 3A. BW, body weight; CMC, sodium carboxymethylcellulose, vehicle control; DEHP, di(2-Ethylhexyl) phthalate; Hep-KO, hepatocyte-specific PPARγ knockout; SD, standard deviation; WT, wild type. *p<0.05, **p<0.01, *** p<0.001, relative to vehicle control [analysis of variance (two-way ANOVA) with post hoc multiple comparison correction using Bonferroni's multiple comparisons test].

Table S15 Clinical chemistry panel in WT and Hep-KO mice [mean ± SD (n)].

Measurements	Treatment	CMC	DEHP
TG(mM)	WT	0.64±0.06 (7)	0.49±0.07 (7)***
	Hep-KO	0.64±0.05 (5)	0.49±0.05 (5)**
CHO(mM)	WT	1.62±0.41 (7)	2.30±0.26 (7)***
	Hep-KO	1.71±0.35 (5)	2.36±0.06 (5)**
CHE(mM)	WT	2.63±0.21 (7)	3.95±0.50 (7)***
	Hep-KO	2.74±0.16 (4)	3.89±0.31 (5)***
ALP(U/L)	WT	72.67±5.05 (6)	93.00±11.25 (7)**
	Hep-KO	70.20±8.07 (5)	96.40±14.84 (5)**
HDLC(mM)	WT	1.22±0.13 (7)	1.57±0.12 (6)***
	Hep-KO	1.19±0.21 (5)	1.58±0.05 (5)***
LDLC(mM)	WT	0.25±0.03 (5)	0.35±0.04 (6)**
	Hep-KO	0.27±0.06 (5)	0.42±0.04 (5)***

Note: Correspond to Figure 3B. ALP, alkaline phosphatase; BW, body weight; CHE, cholinesterase; CHO, cholesterol; CMC, sodium carboxymethylcellulose, vehicle control; DEHP, di(2-Ethylhexyl) phthalate; HDLC, high-density lipoprotein cholesterol; Hep-KO, hepatocyte-specific PPARγ knockout; LDLC, low-density lipoprotein cholesterol; SD, standard deviation; TG, triglycerides; U/L, units per liter; WT, wild type. *p<0.05, **p<0.01, ***p<0.001, relative to vehicle control [analysis of variance (two-way ANOVA) with post hoc multiple comparison correction using Bonferroni's multiple comparisons test].

Table S16 Concentration of hepatic TG in WT and Hep-KO mice [μg/mg tissue; mean ± SD (n)].

Treatment	CMC	DEHP
WT	1.05±0.13 (7)	2.64±0.20 (7)***
Hep-KO	0.88±0.23 (5)	2.71±0.25 (5)***

Note: Correspond to Figure 3C. CMC, sodium carboxymethylcellulose, vehicle control; DEHP, di(2-Ethylhexyl) phthalate; Hep-KO, hepatocyte-specific PPARγ knockout; SD, standard deviation; TG, triglycerides; WT, wild type. *p<0.05, **p<0.01, ***p<0.001, relative to vehicle control [analysis of variance (two-way ANOVA) with post hoc multiple comparison correction using Bonferroni's multiple comparisons test].

Table S17 Hepatic pathological severity evaluation in WT and Hep-KO mice [evaluating scores; mean ± SD (n)].

Treatment	CMC	DEHP
WT	1.29±0.49 (7)	11.29±3.86 (7)***
Hep-KO	1.20±0.45 (5)	10.60±3.44 (5)***

Note: Correspond to Figure 3D. CMC, sodium carboxymethylcellulose, vehicle control; DEHP, di(2-Ethylhexyl) phthalate; Hep-KO, hepatocyte-specific PPARγ knockout; SD, standard deviation; WT, wild type. *p<0.05, **p<0.01, ***p<0.001, relative to vehicle control [analysis of variance (two-way ANOVA) with post hoc multiple comparison correction using Bonferroni's multiple comparisons test].

Table S18 Macrophages evaluation in liver sections from WT and Hep-KO mice [cell number per site; mean ± SD (n)].

	Treatment	**CMC**	**DEHP**
CLEC4F^{+} KCs	WT	102.43±9.85 (7)	50.71±10.05 (7)***
	Hep-KO	98.60±10.01 (5)	46.00±18.73 (5)***
F4/80^{+} macrophages	WT	286.14±26.33 (7)	306.43±26.15 (7)
	Hep-KO	290.60±41.32 (5)	293.20±24.99 (5)

Note: Correspond to Figure 3F. CMC, sodium carboxymethylcellulose, vehicle control; DEHP, di(2-Ethylhexyl) phthalate; Hep-KO, hepatocyte-specific PPARγ knockout; KCs, kupffer cells; SD, standard deviation; WT, wild type. *p<0.05, **p<0.01, ***p<0.001, relative to vehicle control [analysis of variance (two-way ANOVA) with post hoc multiple comparison correction using Bonferroni's multiple comparisons test].

Table S19 Liver weight and liver index in WT and Mac-KO mice [mean ± SD; n=5/group]

	Treatment	**CMC**	**DEHP**
Liver weight(g)	WT	1.36±0.30	1.87±0.20***
	Mac-KO	1.50±0.09	1.70±0.10
Liver index(%BW)	WT	4.60±0.71	6.39±0.16***
	Mac-KO	4.94±0.27	5.55±0.20[a]

Note: Correspond to Figure 4A. BW, body weight; CMC, sodium carboxymethylcellulose,vehicle control; DEHP, di(2-Ethylhexyl) phthalate; Mac-KO, macrophage-specific PPARγ knockout; SD, standard deviation; WT, wild type. *p<0.05, **p<0.01, ***p<0.001, relative to vehicle control; [a]p<0.05, [b]p<0.01, [c]p<0.001, relative to WT DEHP [analysis of variance (two-way ANOVA) with post hoc multiple comparison correction using Tukey's multiple comparisons test].

Table S20 Concentration of hepatic TG in WT and Mac-KO mice [μg/mg tissue; mean ± SD; n=5/group].

Treatment	CMC	DEHP
WT	0.99±0.18	3.09±0.36***
Mac-KO	0.94±0.34	1.55±0.36*,c

Note: Correspond to Figure 4B. CMC, sodium carboxymethylcellulose, vehicle control; DEHP, di(2-Ethylhexyl) phthalate; Mac-KO, macrophage-specific PPARγ knockout; SD, standard deviation; TG, triglycerides; WT, wild type. *p<0.05, **p<0.01, ***p<0.001, relative to vehicle control; [a]p<0.05, [b]p<0.01, [c]p<0.001, relative to WT DEHP [analysis of variance (two-way ANOVA) with post hoc multiple comparison correction using Tukey's multiple comparisons test].

Table S21 Hepatic pathological severity and oil red staining evaluation in WT and Mac-KO mice [evaluating scores; mean ± SD; n=5/group].

	Treatment	CMC	DEHP
Pathological severity	WT	1.40±0.55	12.20±2.49***
	Mac-KO	1.60±0.55	6.60±1.95**,c
Oil red staining intensity	WT	1.20±0.45	11.40±3.13***
	Mac-KO	1.60±0.89	5.60±1.67*,c

Note: Correspond to Figure 4C. CMC, sodium carboxymethylcellulose, vehicle control; DEHP, di(2-Ethylhexyl) phthalate; Mac-KO, macrophage-specific PPARγ knockout; SD, standard deviation; WT, wild type. *p<0.05, **p<0.01, ***p<0.001, relative to vehicle control; [a]p<0.05, [b]p<0.01, [c]p<0.001, relative to WT DEHP [analysis of variance (two-way ANOVA) with post hoc multiple comparison correction using Tukey's multiple comparisons test].

Table S22 M2 macrophages analysis in liver of WT and Mac-KO mice using flow cytometry [% of $CD45^+$ cells; mean ± SD; n=5/group].

	Treatment	**CMC**	**DEHP**
$F4/80^+CD206^+$	WT	16.30±3.26	14.08±2.33**
M2 Macrophages	Mac-KO	16.96±2.01	$22.60±2.62^c$

Note: Correspond to Figure 4D. CMC, sodium carboxymethylcellulose, vehicle control; DEHP, di(2-Ethylhexyl) phthalate; Mac-KO, macrophage-specific PPARγ knockout; SD, standard deviation; WT, wild type. *p<0.05, **p<0.01, ***p<0.001, relative to vehicle control; $^a p$<0.05, $^b p$<0.01, $^c p$<0.001, relative to WT DEHP [analysis of variance (two-way ANOVA) with post hoc multiple comparison correction using Tukey's multiple comparisons test].

Table S23 Macrophages evaluation in liver sections from WT and Mac-KO mice [cell number per site; mean ± SD; n=5/group].

	Treatment	**CMC**	**DEHP**
CLEC4F+	WT	101.60±10.88	46.80±13.16***
Kupffer Cells	Mac-KO	101.60±11.61	117.80±13.74[c]

Note: Correspond to Figure 4E. CMC, sodium carboxymethylcellulose, vehicle control; DEHP, di(2-Ethylhexyl) phthalate; Mac-KO, macrophage-specific PPARγ knockout; SD, standard deviation; WT, wild type. *p<0.05, **p<0.01, ***p<0.001, relative to vehicle control; [a]p<0.05, [b]p<0.01, [c]p<0.001, relative to WT DEHP [analysis of variance (two-way ANOVA) with post hoc multiple comparison correction using Tukey's multiple comparisons test].

Table S24 Monocyte evaluation in liver from WT and Mac-KO mice [% of $CD45^+$cells; mean ± SD; n=5/group]

	Treatment	**CMC**	**DEHP**
$CD11b^+CCR2^+Ly6c^{high}$	WT	1.90±0.67	3.88±0.83***
Inflammatory monocyte	Mac-KO	1.15±0.30	2.26±0.53[b]
$CD11b^+CCR2^+Ly6c^{low}$	WT	11.45±2.41	12.27±1.84
Patrolling monocyte	Mac-KO	12.81±1.22	17.47±2.92[b]

Note: Correspond to Figure 4F. CMC, sodium carboxymethylcellulose, vehicle control; DEHP, di(2-Ethylhexyl) phthalate; Mac-KO, macrophage-specific PPARγ knockout; SD, standard deviation; WT, wild type. *p<0.05, **p<0.01, ***p<0.001, relative to vehicle control; [a]p<0.05, [b]p<0.01, [c]p<0.001, relative to WT DEHP [analysis of variance (two-way ANOVA) with post hoc multiple comparison correction using Tukey's multiple comparisons test].

Table S25 M2 macrophages polarization evaluation in BMDM from WT and Mac-KO mice [$CD206^+$ cells (%); mean ± SD; n=15 technical replicates/treatment].

Treatment	CT(DMSO)	DEHP	MEHP
WT	90.13±2.00	68.14±4.50***	73.78±4.59***
Mac-KO	92.55±2.43	76.18±3.88^c	84.04±4.46^c

Note: Correspond to Figure 5A. BMDM, bone marrow derived macrophages; CT, vehicle control; DEHP, di(2-Ethylhexyl) phthalate; DMSO, dimethyl sulfoxide; MEHP, mono-2-ethylhexyl phthalate; Mac-KO, macrophage-specific PPARγ knockout; SD, standard deviation; WT, wild type. *p<0.05, **p<0.01, ***p<0.001, relative to vehicle control. $^a p$<0.05, $^b p$<0.01, $^c p$<0.001, relative to WT DEHP or WT MEHP [analysis of variance (two-way ANOVA) with post hoc multiple comparison correction using Tukey's multiple comparisons test].

Table S26 Relative expression of DEGs associated with M2 macrophages in MEHP treated macrophages [Z scores; n=3/treatment; provided as Excel Table S26].

Table S27 Relative expression of DEGs associated with PPAR pathway in MEHP treated macrophages [Z scores; n=3/treatment; provided as Excel Table S27].

Table S28 Characteristics of PPRE-THP-1 cells derived M2 macrophages [Mean stain area (μm2); mean ± SD; n=2/subtype].

Treatment	CD209	PPRE	CD36	LD
M0	21.90±0.14	37.09±5.29	115.42±25.90	116.87±24.68
M1	64.16±2.28*	53.16±8.15	104.42±15.16	129.52±32.37
M2	346.11±5.79**	88.42±6.98**	204.92±0.64**	215.70±4.13**

Note: Correspond to Figure 5E. LD, lipid droplet; PPRE,peroxisome proliferator-activated receptor response elements; SD, standard deviation. *p<0.05, **p<0.01, ***p<0.001, relative to vehicle control [analysis of variance (one-way ANOVA) with post hoc multiple comparison correction using Bonferroni's multiple comparisons test].

Table S29 Dose response curves of PPRE/CD209/LD in DEHP/MEHP treated M2 macrophages [% of control; mean, n=3/treatment].

Concentration	DEHP			MEHP		
(log10, μM)	CD209	PPRE	LD	CD209	PPRE	LD
2.30	49.23	73.13	32.05	39.04	84.41	43.07
2.00	67.16	/	39.74	52.23	81.93	61.16
1.70	/	82.40	26.68	65.51	82.90	46.08
1.40	56.72	/	/	73.63	77.84	57.08
1.10	71.68	79.55	42.93	66.98	/	63.00
0.80	64.71	86.07	50.59	82.05	/	78.72
0.49	85.89	85.18	/	94.20	86.56	89.05
0.19	78.34	92.57	71.80	/	86.99	/
0.00	100.00	100.00	100.00	100.00	100.00	100.00

Note: Correspond to Figure 5F. DEHP, di(2-Ethylhexyl) phthalate; LD, lipid droplet; MEHP, mono-2-ethylhexyl phthalate; PPRE,peroxisome proliferator-activated receptor response elements.

Table S30 Data for Figure 5G: Dose response curves of CD209 in PPARα/γ agonists treated M2 macrophages [Mean stain area (μm^2); mean; n=3/treatment].

Concentration (log10, μM)	WY	RGZ	MEHP	GW7647
1.40	116.19	26.99	37.79	/
1.10	100.02	50.91	49.02	/
0.80	119.79	60.79	56.73	/
0.49	95.07	61.34	73.97	/
0.19	93.99	58.64	76.44	/
-0.11	69.17	61.09	76.12	/
-0.41	71.35	71.35	71.35	/
1.30	/	/	/	202.88
1.00	/	/	/	195.04
0.70	/	/	/	193.10
0.40	/	/	/	180.27
0.10	/	/	/	122.67
-0.20	/	/	/	/
-0.51	/	/	/	95.27
-0.81	/	/	/	71.35

Note: Correspond to Figure 5G. GW7647, PPARα agonist; MEHP, mono-2-ethylhexyl phthalate; RGZ, rosiglitazone, PPARγ agonist; WY, WY14643, PPARα agonist.

Table S31 Data for Figure 5H: Dose response curves of CD209 in PPARα/γ antagonists treated M2 macrophages [Mean stain area (μm^2); mean, n=3/treatment]

Concentration (log10, μM)	**GW6471**	**GW9662**	**T0070907**
0.10	62.84	83.37	93.42
-0.20	68.33	82.01	91.64
-0.51	76.97	82.45	90.49
-0.81	77.89	80.13	83.53
-1.11	75.14	69.83	78.47

Note: Correspond to Figure 5H. GW6471, PPARα antagonist; GW9662, PPARγ antagonist; T0070907, PPARγ antagonist and inverse agonist.

Table S32 Response of CD209/CD36/LD in MEHP treated M2 macrophages with/without PPARα/γ antagonists [Mean stain area (μm^2); mean ± SD (n)].

Treatment	CT(DMSO)	MEHP	M+GW6471	M+GW9662
CD209	153.98±29.47 (4)	98.39±26.21 (3)*	45.29±4.79 (3)***,3	111.46±14.36 (3)
CD36	52.09±2.50 (4)	35.10±3.04 (5)**	18.19±4.29 (5)***,2	41.96±9.78 (5)
LD	347.32±13.57 (4)	296.67±39.66 (4)*	233.82±15.60 (4)**,1	374.59±13.60 (4)2

Note: Correspond to Figure 5I. CT, vehicle control; DMSO, dimethyl sulfoxide; GW6471, PPARα antagonist; GW9662, PPARγ antagonist; MEHP, mono-2-ethylhexyl phthalate; SD, standard deviation. *p<0.05, **p<0.01, ***p<0.001, relative to vehicle control; [1]p<0.05, [2]p<0.01,[3]p<0.001, relative to MEHP treatment [analysis of variance (one-way ANOVA) with post hoc multiple comparison correction using Bonferroni's multiple comparisons test].

Table S33 Data for Figure 6A: Transcriptomic profiling of livers from different mice models [DEGs; provided as Excel Table S33].

Table S34 Data for Figure 6B: Relative expression of DEGs associated with lipid metabolism in liver from different mice models [Z scores; n=4-6/group; provided as Excel Table S34].

Table S35 Pathway enrichment analysis of DEGs in liver from different mice models [enrichment scores].

Pathways	WT	Hep-KO	Mac-KO
PPAR signaling pathway	11.52	11.30	9.46
Fatty acid degradation	10.75	10.90	9.17
Retinol metabolism	7.59	7.05	8.18
Biosynthesis of unsaturated fatty acids	6.65	2.74	5.87
Chemical carcinogenesis	6.45	3.75	3.05
Oxidative phosphorylation	5.24	4.98	0.00
Fatty acid metabolism	4.68	1.96	3.87
Valine, leucine and isoleucine degradation	4.46	2.82	3.74
Steroid hormone biosynthesis	3.99	0.00	4.17
Arachidonic acid metabolism	3.92	4.84	6.48

Note: Correspond to Figure 6C. DEGs, differentially expressed genes; Hep-KO, hepatocyte-specific PPARγ knockout; Mac-KO, macrophage-specific PPARγ knockout; WT, wild type.

Table S36 Data for Figure 6D: GO analysis of DEGs in livers from different mice models [provided as Excel Table S36].

Table S37 Superclass constitution of lipid metabolites in liver from different mice models [lipid counts; average ratio (DEHP/CT ratio)].

Mice model	**WT**		**Hep-KO**		**Mac-KO**	
NEG	LC	AR	LC	AR	LC	AR
Glycerophospholipids[GP]	6635	1.89	5947	2.03	4579	1.39
Glycerolipids[GL]	529	7.01	514	4.94	301	2.72
Fatty Acyls[FA]	1794	2.89	2127	1.95	3089	3.48
Sphingolipids[SP]	324	1.44	291	1.54	225	1.64
Sterol Lipids[ST]	124	3.37	205	1.89	209	2.40
Polyketides[PK]	373	1.08	218	1.43	307	1.60
Prenol Lipids[PR]	162	3.28	156	6.81	120	4.32
Saccharolipids[SL]	3	3.03	2	1.69	3	2.73
POS						
Glycerophospholipids[GP]	7389	1.91	6040	1.39	6102	1.91
Glycerolipids[GL]	3708	0.84	2917	1.03	4750	0.82
Fatty Acyls[FA]	1656	1.07	1146	1.41	800	1.03
Sphingolipids[SP]	593	1.74	686	2.80	313	1.23
Sterol Lipids[ST]	399	1.90	311	1.74	215	1.61
Polyketides[PK]	249	1.32	233	1.36	177	1.01
Prenol Lipids[PR]	180	1.38	382	0.99	164	0.88
Saccharolipids[SL]	9	1.82	7	1.60	9	1.10

Note: Correspond to Figure 6E. AR, average ratio (DEHP/CT ratio); DEHP, di(2-Ethylhexyl) phthalate; Hep-KO, hepatocyte-specific PPARγ knockout; LC, lipid counts; Mac-KO, macrophage-specific PPARγ knockout; NEG, negative ion mode; POS, postive ion mode.

Table S38 Data for Figure 6F: Class constitution of lipid metabolites in livers from different mice models [lipid counts; average ratio (DEHP/CT ratio); provided as Excel Table S38].

Table S39 Evaluation of mitochondrial OXPHOS, fatty acid uptake and LD in HepG2 cells treated with MEHP with/without specific inhibitors [Mean stain area (μm^2); mean±SD; n=5/treatment].

Determination	TMRE	BODIPY FL C12	LD
CT(DMSO)	20.96±5.60	25.51±2.65	14.53±3.85
MEHP	59.46±6.39***	49.27±6.79***	33.93±5.52***
MEHP+IACS	11.90±2.42[3]	20.53±4.90[3]	20.89±2.51[2]
MEHP+VLX	31.93±9.49[3]	28.90±3.68[3]	22.05±4.35[1]
MEHP+3-NP	33.53±8.19[3]	25.03±3.73[3]	15.63±7.11[3]
MEHP+IL-1RA	39.07±5.34**[,3]	26.12±6.19[3]	18.45±7.00[2]

Note: Correspond to Figure 7A, 7B. 3-NP, 3-Nitropropanoic acid (2 mM); CT, vehicle control; DMSO, dimethyl sulfoxide; IACS, IACS-10759 (10 nM); IL-1RA (200 ng/ml); LD, lipid droplet; MEHP, mono-2-ethylhexyl phthalate (200 μM); OXPHOS, oxidative phosphorylation; TMRE, tetramethylrhodamine ethyl ester, mitochondrial membrane potential indicator; SD, standard deviation; VLX, VLX600 (1 μM). *p<0.05, **p<0.01, ***p<0.001, relative to vehicle control; [1]p<0.05, [2]p<0.01,[3]p<0.001, relative to MEHP treatment [analysis of variance (one-way ANOVA) with post hoc multiple comparison correction using Tukey's multiple comparisons test].

Table S40 Evaluation of mitochondrial OXPHOS and LD in HepG2 cells treated with MEHP with/without M2 macrophages [Mean stain area (μm2); mean ± SD; n=5/treatment].

With/without M2	Treatment	TMRE	MitoSOX	LD
HepG2	CT(DMSO)	145.98±3.62	51.79±3.00	60.98±4.32
(without M2)	MEHP	163.29±3.05**	56.49±1.79***	117.28±17.67***
Co-M2	CT(DMSO)	129.66±9.46	37.76±2.30	59.38±7.07
(HepG2 with M2)	MEHP	140.69±11.12[3]	37.27±4.53[3]	88.42±4.45[3]

Note: Correspond to Figure 7C. CT, vehicle control; DMSO, dimethyl sulfoxide; LD, lipid droplet; MEHP, mono-2-ethylhexyl phthalate (200 μM); mitoSOX, mitochondrial superoxide, mitochondrial reactive oxygen species indicator; OXPHOS, oxidative phosphorylation; TMRE, tetramethylrhodamine ethyl ester, mitochondrial membrane potential indicator; SD, standard deviation. *p<0.05, **p<0.01, ***p<0.001, relative to vehicle control; [1]p<0.05, [2]p<0.01,[3]p<0.001, relative to MEHP treatment [analysis of variance (two-way ANOVA) with post hoc multiple comparison correction using Tukey's multiple comparisons test].

Table S41 Relative expression of DEGs associated with OXPHOS in HepG2 cells treated with MEHP with/without M2 macrophages [Z scores; n=2/treatment].

DEGs	HepG2		MEHP-HepG2		MEHP-HepG2-Co-M2	
	R-1	R-2	R-1	R-2	R-1	R-2
MT-ATP6	-0.34	-0.06	1.68	0.53	-0.63	-1.17
MT-ND2	-0.13	-0.03	1.43	0.84	-1.16	-0.95
MT-CYB	0.09	0.15	1.27	0.78	-0.94	-1.36
MT-ND4L	-0.20	0.88	1.05	0.52	-0.73	-1.51
ATP6V0E2	0.44	0.34	1.03	0.57	-0.72	-1.67
MT-ND1	-0.80	-0.73	1.69	0.72	-0.30	-0.59
MT-CO1	-1.00	-0.77	1.65	0.44	0.30	-0.62
MT-ND5	-0.68	-1.05	1.38	0.64	0.59	-0.88
MT-ND6	-1.02	-1.23	1.36	0.42	0.63	-0.15
MT-ATP8	0.03	-0.70	0.30	0.55	1.34	-1.52
ATP6V0A2	0.34	-0.01	-0.58	1.74	-0.28	-1.20

Note: Correspond to Figure 7D. DEGs, differentially expressed genes; MEHP, mono-2-ethylhexyl phthalate (200 μM); R, replicate.

Table S42 Relative expression of DEGs associated with glycolysis in HepG2 cells treated with MEHP with/without M2 macrophages [Z scores; n=3/treatment].

DEGs	MEHP-HepG2			MEHP-HepG2-Co-M2		
	R-1	R-2	R-3	R-1	R-2	R-3
ALDOC	-0.97	-0.84	-0.90	1.09	0.92	0.71
LDHA	-1.01	-0.71	-1.01	0.94	0.96	0.81
HK1	-1.40	-0.53	-0.67	0.91	0.72	0.98
ENO2	-1.02	-0.49	-1.08	0.76	1.29	0.55
ENO1	-0.93	-0.66	-1.03	0.98	1.23	0.42
PKM	-0.87	-0.94	-0.87	1.08	1.08	0.52
PGM1	-0.62	-1.12	-0.84	1.31	0.40	0.87
HK2	-0.39	-1.12	-0.84	1.30	-0.05	1.09
PGK1	-0.59	-0.99	-0.69	1.37	-0.22	1.12
TPI1	-0.84	-0.68	-1.11	1.12	1.08	0.43
GAPDH	-1.01	-0.38	-1.01	0.63	1.54	0.22
PFKL	-1.09	-0.38	-0.88	0.69	1.55	0.11
PFKP	-0.56	-1.16	-0.61	1.62	0.55	0.16
PFKFB4	-0.92	-0.80	-1.01	0.95	0.90	0.88
PFKFB3	-0.70	-0.95	-1.04	1.05	0.61	1.03
MPI	-1.14	-0.64	-0.71	0.69	1.49	0.32
ENOSF1	-0.98	-0.35	-1.09	0.44	1.52	0.47
PFKFB1	-1.00	-0.51	-1.00	0.19	1.27	1.04

Note: Correspond to Figure 7E. DEGs, differentially expressed genes; MEHP, mono-2-ethylhexyl phthalate (200 μM); R, replicate.

Table S43 Relative expression of DEGs associated with lipid metabolism in HepG2 cells treated with MEHP with/without M2 macrophages [Z scores; n=3/treatment].

Pathways	DEGs	MEHP-HepG2			MEHP-HepG2-Co-M2		
		R-1	R-2	R-3	R-1	R-2	R-3
Glycerolipid metabolism	*ALDH1B1*	1.16	0.43	0.88	-0.23	-1.38	-0.86
	GPD1L	0.83	0.17	0.98	-0.22	-1.81	0.04
	PCYT1A	0.97	0.33	0.98	-0.29	-1.68	-0.30
	GPD1	0.94	0.79	0.86	-1.27	-0.31	-1.02
	ETNK2	0.21	0.66	1.50	-0.94	-1.13	-0.31
	PCYT1B	0.68	0.42	1.41	-0.51	-0.73	-1.26
	ETNPPL	0.83	0.90	0.75	-0.56	-0.33	-1.58
	PLA2G12B	1.02	0.43	0.89	-0.15	-1.63	-0.56
	PLA2G12A	1.22	0.09	0.92	-1.33	-0.93	0.03
	PLPP3	1.06	0.30	0.78	-0.22	-1.76	-0.17
	PLPP1	0.71	0.98	0.98	-0.70	-1.24	-0.74
	GPAM	1.03	0.35	0.87	-0.46	-1.68	-0.11
	AGPAT3	1.27	0.69	0.67	-0.60	-1.07	-0.97
	DGKK	0.96	0.12	0.87	-0.28	-1.80	0.13
Fatty acid metabolism	*ADH6*	0.92	0.99	0.48	-0.40	-1.63	-0.36
	ADH4	0.72	0.85	1.05	-0.38	-1.26	-0.97
	EHHADH	0.89	0.28	0.64	-0.08	-1.92	0.18
	ACSL1	1.04	0.15	0.77	-0.08	-1.82	-0.06
	HACD2	0.87	0.13	0.85	-0.28	-1.83	0.26
	FADS1	0.82	-0.19	0.99	0.14	-1.81	0.05
	ICMT	0.88	0.78	1.00	-0.51	-1.17	-0.99
	IDI1	0.90	0.37	0.67	-0.27	-1.87	0.20
	HMGCR	0.93	0.15	0.72	0.04	-1.90	0.06
	ACAT2	0.86	0.74	1.09	-0.63	-0.96	-1.10
	HMGCS1	1.02	0.10	0.73	-0.03	-1.85	0.03
	MCAT	0.75	0.92	0.89	-1.34	-0.27	-0.95
	FASN	1.11	0.57	0.99	-1.09	-0.73	-0.85

Note: Correspond to Figure 7F. DEGs, differentially expressed genes; MEHP, mono-2-ethylhexyl phthalate (200 μM); R, replicate.

Table S44 Body weight fluctuation in DEHP treated mice [g; mean ± SD; n=10/group].

Dose group	0 mg/kg BW	625 mg/kg BW	1250 mg/kg BW	2500 mg/kg BW
Week 0	22.4±1.2	23.1±0.8	22.8±1.2	22.9±0.8
Week 1	22.4±1.1	23.4±1.2	22.9±0.8	23.1±1.1
Week 2	23.1±1.3	22.7±1.4	23.5±1.2	22.8±1.2
Week 3	22.9±1.2	23.4±1.2	22.8±1.1	22.5±0.9
Week 4	22.9±1.1	24.0±0.0	23.0±1.0	22.0±0.9

Note: Correspond to Figure S2A. BW, body weight; DEHP, di(2-Ethylhexyl) phthalate; SD, standard deviation. *p<0.05, **p<0.01, ***p<0.001, relative to vehicle control [analysis of variance (one-way ANOVA) with post hoc multiple comparison correction using Dunnett's multiple comparisons test].

Table S45 Data for Figure S2B: Enriched KEGG pathways (level 2) in DEHP treated mice [number of genes; provided as Excel Table S45].

Table S46 Relative expression of DEGs associated with lipid metabolism in HepG2 cells treated with MEHP [Z scores; n=3/treatment].

Pathways	DEGs	HepG2-CT			HepG2-MEHP		
		R-1	R-2	R-3	R-1	R-2	R-3
Glycerolipid metabolism	*PLA2G3*	-1.03	-0.18	-1.25	0.51	0.68	1.27
	AGPAT2	-0.98	-0.51	-0.83	-0.15	1.38	1.08
	LPCAT3	-1.07	-0.31	-0.85	1.14	-0.21	1.30
	AKR1B10	-0.71	-0.79	-1.16	1.13	0.57	0.97
	PLA2G12A	-1.13	0.52	-0.51	1.35	-0.94	0.71
	PLPP3	-0.82	0.54	0.15	1.34	-1.46	0.25
	PLPP5	-0.69	-1.26	-0.36	-0.02	1.39	0.93
	LPIN1	-0.59	-1.50	-0.05	1.16	-0.05	1.02
Fatty acid metabolism	*FADS1*	-0.85	-0.96	-0.78	1.08	0.29	1.22
	TECR	-0.44	-0.62	-0.76	-0.58	1.75	0.66
	FASN	-1.16	-0.49	-0.94	1.16	0.43	1.00
	ACADVL	-0.81	-0.88	-0.86	0.53	1.50	0.53
	ACAT2	-0.81	-1.06	-0.84	0.87	0.75	1.09
	ACAA2	-1.11	-1.21	-0.13	1.10	0.96	0.38
	FDPS	-0.75	-0.88	-1.04	1.20	0.90	0.57
	MVD	-0.97	-0.83	-0.86	0.69	1.32	0.65
	IDI1	-0.72	-0.99	-0.87	1.34	0.34	0.91
	HMGCR	-0.42	-0.65	-0.17	1.57	-1.13	0.79
	MVK	-0.80	-0.79	-1.06	0.61	1.31	0.73
Steroid biosynthesis	*EBP*	-0.52	-0.96	-0.70	0.03	1.78	0.38
	DHCR7	-0.89	-0.81	-1.03	0.89	0.90	0.94
	SQLE	-0.78	-0.89	-0.83	1.33	0.10	1.07
	MSMO1	-0.71	-0.98	-0.91	1.40	0.68	0.51
	NSDHL	-0.32	-1.01	-1.02	0.73	1.51	0.10
	TM7SF2	-1.09	-0.64	-0.62	0.39	1.67	0.28
	SC5D	-0.77	-1.26	-0.19	1.41	-0.09	0.89
	HSD17B7	-0.29	-1.05	-1.20	0.47	1.10	0.97
	AKR1C2	-0.89	-0.84	-0.77	0.20	1.48	0.83
	AKR1C1	-1.02	-1.09	-0.43	0.31	1.23	1.00
	CYP1A1	-0.89	-0.85	-0.91	0.56	0.75	1.33

Note: Correspond to Figure S2C. DEGs, differentially expressed genes; MEHP, mono-2-ethylhexyl phthalate (200 μM); R, replicate.

Table S47 Relative expression of DEGs associated with PPAR pathway in DEHP treated mice [Z scores; n=6/group; provided as Excel Table S47].

Table S48 Pathway enrichment analysis of DEGs in HepG2 cells treated with MEHP [n=3/treatment].

Pathway	**Counts**	**Gene Ratio**	**P*adj***
Fatty acid metabolism	12	12/155	2.30E-07
PPAR signaling pathway	11	11/155	5.25E-05
Ferroptosis	8	8/155	0.00029333
Biosynthesis of unsaturated fatty acids	6	6/155	0.000666895
Terpenoid backbone biosynthesis	6	6/155	0.000746958
Fatty acid degradation	7	7/155	0.002394125
Peroxisome	9	9/155	0.006369618

Note: Correspond to Figure S2E. DEGs, differentially expressed genes; MEHP, mono-2-ethylhexyl phthalate (200 μM).

Table S49 Clinical chemistry panel in WT and Mac-KO mice [mean ± SD (n)].

Measurements	Treatment	CMC	DEHP
TG(mM)	WT	0.68±0.07 (5)	0.38±0.10 (5)**
	Mac-KO	0.60±0.11 (5)	0.66±0.05 (5)[a]
CHO(mM)	WT	1.14±0.07 (5)	2.08±0.30 (5)***
	Mac-KO	1.37±0.07 (3)	1.77±0.14 (4)[a]
CHE(mM)	WT	2.97±0.38 (5)	4.07±0.30(5)***
	Mac-KO	3.34±0.19 (3)	3.82±0.15 (5)
ALP(U/L)	WT	102.83±7.57 (5)	150.86±23.18 (5)***
	Mac-KO	113.00±2.00 (3)	118.33±16.99 (5)[a]
HDLC(mM)	WT	0.71±0.07 (5)	1.23±0.19 (5)***
	Mac-KO	0.88±0.05 (3)	1.12±0.09 (5)
LDLC(mM)	WT	1.47±0.03 (5)	1.76±0.24 (5)**
	Mac-KO	1.53±0.02 (3)	1.66±0.10 (5)

Note: Correspond to Figure S4A. ALP, alkaline phosphatase; CHE, cholinesterase; CHO, cholesterol; CMC, sodium carboxymethylcellulose, vehicle control; DEHP, di(2-Ethylhexyl) phthalate; HDLC, high-density lipoprotein cholesterol; LDLC, low-density lipoprotein cholesterol; Mac-KO, macrophage-specific PPARγ knockout; SD, standard deviation; TG, triglycerides; U/L, units per liter; WT, wild type. *p<0.05, **p<0.01, ***p<0.001, relative to vehicle control; [a]p<0.05, [b]p<0.01, [c]p<0.001, relative to WT DEHP [analysis of variance (two-way ANOVA) with post hoc multiple comparison correction using Bonferroni's multiple comparisons test].

Table S50 Macrophages and neutrophils analysis in liver of WT and Mac-KO mice using flow cytometry [% of $CD45^+$ cells; mean ± SD (n)].

	Treatment	**CMC**	**DEHP**
$CD11b^{high}F4/80^{low}$	WT	8.89±1.00 (5)	12.80±0.94 (5)***
Macrophages	Mac-KO	4.83±0.43 (5)	9.47±1.35 (5)***,[b]
$CD11b^{low}F4/80^{high}$	WT	24.94±3.93 (5)	21.74±3.50 (5)*
Macrophages	Mac-KO	27.30±2.48 (5)	31.22±2.78 (5)[b]
$CD11b^{high}F4/80^{-}Ly6g^{+}$	WT	4.89±1.89 (5)	4.19±0.25 (5)
Neutrophils	Mac-KO	3.66±1.01 (4)	4.10±2.03 (5)

Note: Correspond to Figure S4B. CMC, sodium carboxymethylcellulose, vehicle control; DEHP, di(2-Ethylhexyl) phthalate; Mac-KO, macrophage-specific PPARγ knockout; SD, standard deviation; WT, wild type. *p<0.05, **p<0.01, ***p<0.001, relative to vehicle control; [a]p<0.05, [b]p<0.01, [c]p<0.001, relative to WT DEHP [analysis of variance (two-way ANOVA) with post hoc multiple comparison correction using Tukey's multiple comparisons test].

Table S51 Macrophages featured cytokines analysis in liver of WT and Mac-KO mice using flow cytometry [pg/mg protein; mean ± SD; n=5].

Subtype	Cytokine	Treatment	CMC	DEHP
M1 macrophages	IL-12p70	WT	8.61±2.90	23.73±4.30***
		Mac-KO	11.45±3.22	12.43±2.08[b]
	IL-18	WT	39.53±10.10	63.02±7.30***
		Mac-KO	54.88±7.96	36.13±9.30[b]
M2 macrophages	IL-10	WT	77.52±7.39	52.44±6.31***
		Mac-KO	67.11±4.54	62.22±5.66
	IL-23	WT	33.07±5.48	24.05±4.04**
		Mac-KO	30.91±1.15	32.41±3.52[c]

Note: Correspond to Figure S4C. CMC, sodium carboxymethylcellulose, vehicle control; DEHP, di(2-Ethylhexyl) phthalate; Mac-KO, macrophage-specific PPARγ knockout; SD, standard deviation; WT, wild type. *p<0.05, **p<0.01, ***p<0.001, relative to vehicle control; [a]p<0.05, [b]p<0.01, [c]p<0.001, relative to WT DEHP [analysis of variance (two-way ANOVA) with post hoc multiple comparison correction using Tukey's multiple comparisons test].

Table S52 $CD69^+$ M1 macrophages evaluation in BMDM from WT and Mac-KO mice [mean stain area (μm2); mean±SD (n)].

Treatment	CT(DMSO)	DEHP	MEHP
WT	131.62±10.59 (11)	126.57±13.17 (14)	121.86±12.28 (11)
Mac-KO	129.17±17.18 (12)	117.85±13.47 (12)	133.54±15.80 (9)

Note: Correspond to Figure S5B. n, technical replicates. CT, vehicle control; DEHP, di(2-Ethylhexyl) phthalate; DMSO, dimethyl sulfoxide; Mac-KO, macrophage-specific PPARγ knockout; MEHP, mono-2-ethylhexyl phthalate; SD, standard deviation; WT, wild type. *p<0.05, **p<0.01, ***p<0.001, relative to vehicle control; $^a p$<0.05, $^b p$<0.01, $^c p$<0.001, relative to WT DEHP or WT MEHP [analysis of variance (two-way ANOVA) with post hoc multiple comparison correction using Bonferroni's multiple comparisons test].

Table S53 Relative expression of DEGs associated with M1 macrophages in MEHP treated macrophages [Z scores; n=3/treatment; provided as Excel Table S53].

Table S54 Macrophages lipid metabolism analysis in liver of WT and Mac-KO mice using flow cytometry [% of $CD45^+$ cells; mean ± SD; n=5/treatment].

	Treatment	**CMC**	**DEHP**
$CD36^{high}$	WT	6.77±2.86	8.67±2.50
Macrophages	Mac-KO	7.55±1.24	14.30±2.80[a]
LD^{high}	WT	13.26±2.23	12.09±2.06
Macrophages	Mac-KO	13.90±0.87	19.24±2.66[c]

Note: Correspond to Figure S5D. CMC, sodium carboxymethylcellulose, vehicle control; DEHP, di(2-Ethylhexyl) phthalate; Mac-KO, macrophage-specific PPARγ knockout; SD, standard deviation; WT, wild type. *p<0.05, **p<0.01, ***p<0.001, relative to vehicle control; [a]p<0.05, [b]p<0.01, [c]p<0.001, relative to WT DEHP [analysis of variance (two-way ANOVA) with post hoc multiple comparison correction using Tukey's multiple comparisons test].

Supplemental Figures

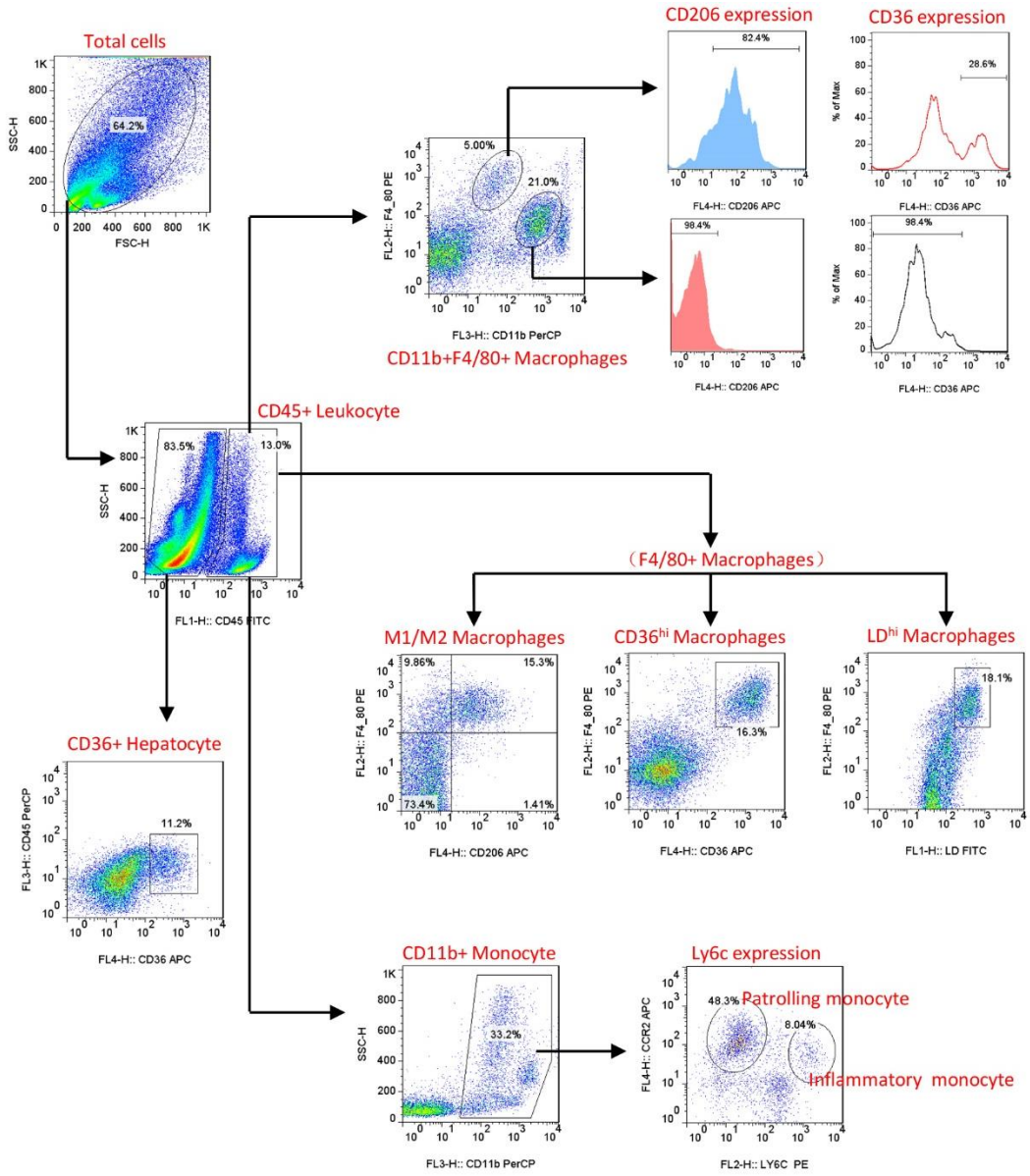


Figure S1. Gating strategy for flow cytometry of mouse liver.

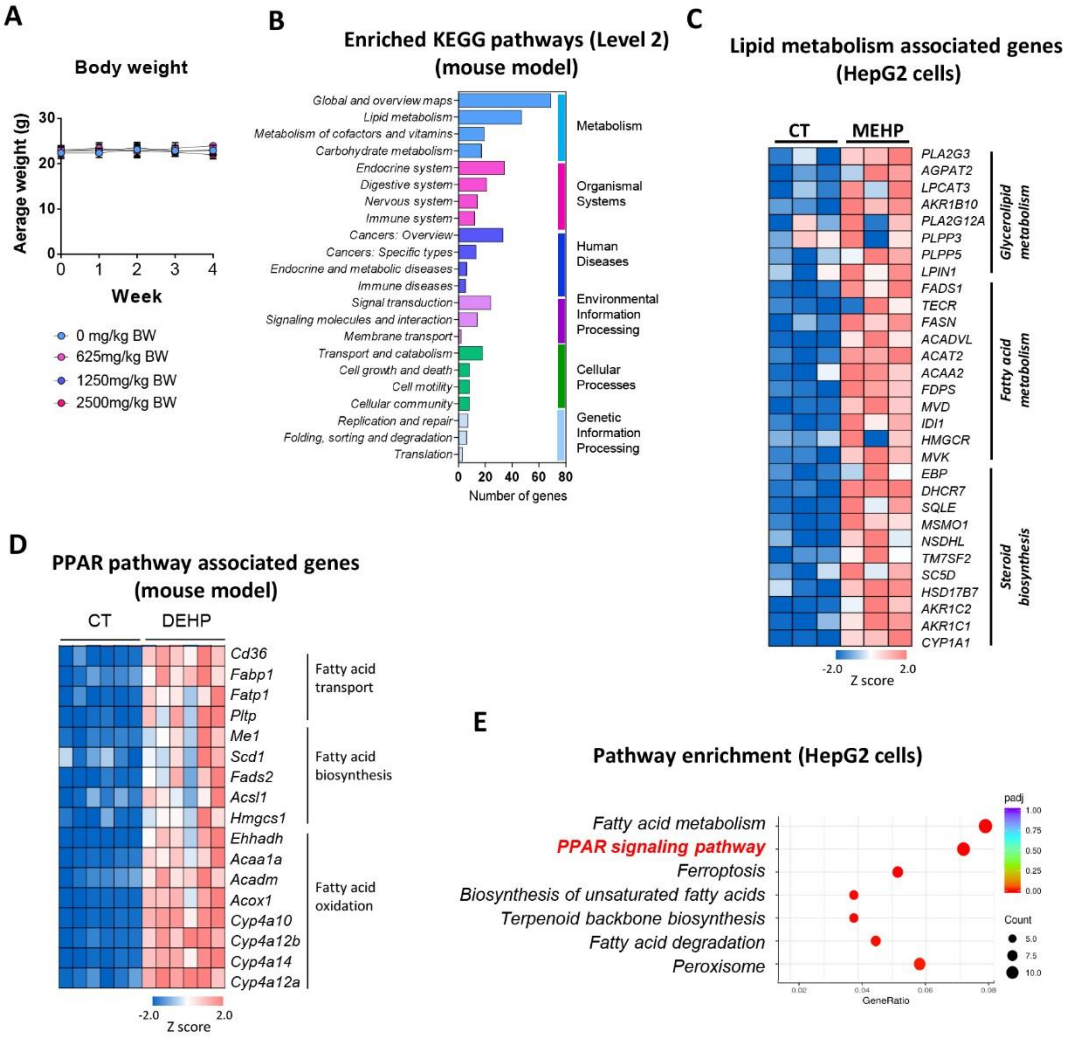


Figure S2. The effect of DEHP on hepatic lipid metabolism.

(A) Body weight of mice in the dose-response study of DEHP. C57BL/6J male mice were treated with 0.5% (wt/vol) sodium carboxymethylcellulose (CMC, vehicle control) or different doses of DEHP (625, 1250, and 2500 mg/kg bw) by daily gavage for 28 days. Data were expressed as mean±SD (n=10/group).The data for Figure S2A are located in Table S44.

(B) Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment (level 2) of differentially expressed genes (DEGs) from livers of mice treated with CMC (vehicle control, CT) or DEHP (625 mg/kg bw) for 28 days (n=6/group).The data for

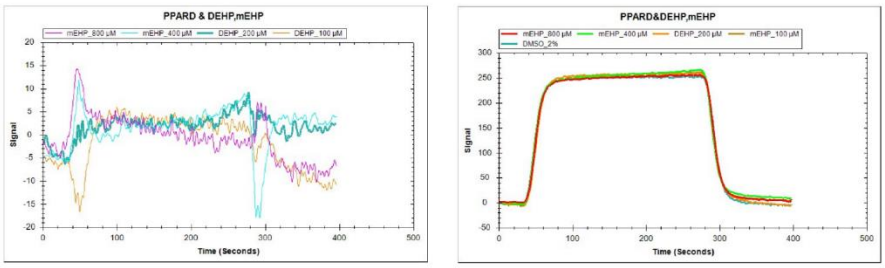
Figure S2B are located in Table S45.

(C) Heatmap of gene expression associated with PPAR signaling pathway in HepG2 cells. The cells were treated with MEHP (200 μM) for 24 h in triplicate wells (n=3/treatment). After treatment, cells were collected for RNA sequencing. The data for Figure S2C are located in Table S46.

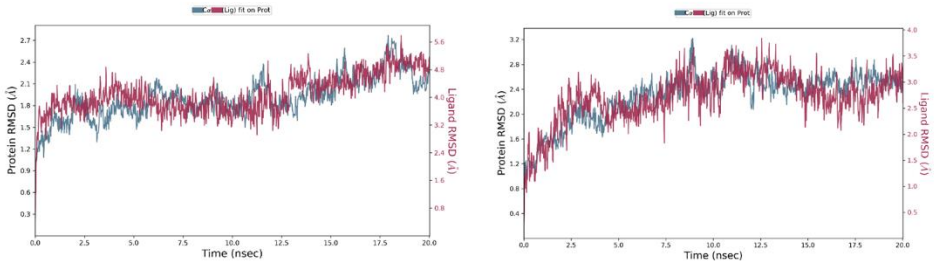
(D) Heatmap of gene expression associated with PPAR signaling pathway in mice model. C57BL/6J male mice treated with CMC (vehicle control, CT) or DEHP (625 mg/kg bw) for 28 days (n=6/group).The data for Figure S2D are located in Table S47.

(E) KEGG pathway enrichment for the HepG2 model. The cells were treated with MEHP (200 μM) for 24 h in triplicate wells (n=3/treatment). After treatment, cells were collected for RNA sequencing. The data for Figure S2E are located in Table S48.

A



B



RMSD (PPARα) RMSD (PPARγ)

C

Comparison of the binding free energy of different complexes

Complex	ΔEvdw (kcal/mol)	ΔEele energy (kcal/mol)	ΔEpb (kcal/mol)	ΔEcavity (kcal/mol)	ΔGgas (kcal/mol)	ΔGsol (kcal/mol)	ΔGbinding (kcal/mol)
PPARα	-0.69	-9.29	2.50	-0.12	-9.98	2.38	-7.60
PPARγ	-1.07	-9.33	2.24	-0.17	-10.40	2.07	-8.33

VDWAALS = van der Waals contribution from molecular minimization (MM).
EEL = electrostatic energy as calculated by the MM force field.
EPB = the electrostatic contribution to the solvation free energy calculated by PB.
ECAVITY = nonpolar contribution to the solvation free energy calculated by an empirical model.
DELTA G binding = final estimated binding free energy calculated from the terms above. (kCal/mol)
ΔGgas = ΔEvdw + ΔEele, ΔGsol = ΔEpb + ΔEcavity, ΔGbinding = ΔGgas + ΔGsol

Figure S3. Activation of PPAR isoforms by DEHP and MEHP at the molecular level.

(A) Sensorgram showing the binding response of PPARδ with DEHP or MEHP as determined by surface plasmon resonance (SPR) analysis.

(B) Root mean square deviation (RMSD) plots showing the stability of optimal docking complex.

(C) The binding free energy of MEHP with PPARα and PPARγ in molecular docking and simulation.

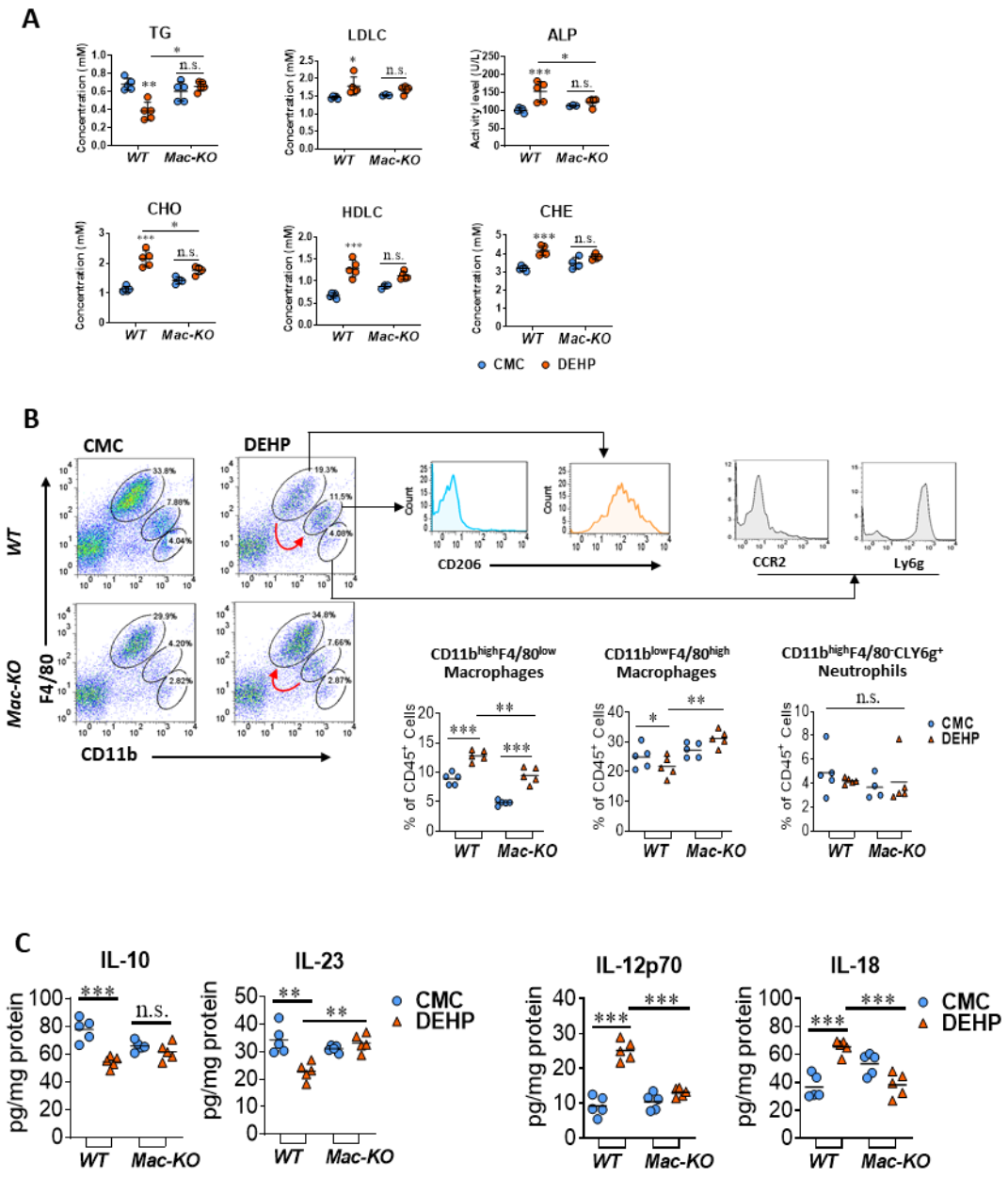


Figure S4. The function of PPARγ in hepatic macrophages.

Wild-type (WT, n=5/group) and macrophage-specific PPARγ knockout (Mac-KO, n=5/group) C57BL/6J male mice were treated with 0.5% (wt/vol) sodium carboxymethylcellulose (CMC, vehicle control) or DEHP (625 mg/kg bw) by daily gavage for 28 days.

(A) Plasma level of triglyceride (TG), cholesterol (CHO), high-density lipoprotein cholesterol (HDLC), low-density lipoprotein cholesterol (LDLC), alkaline phosphatase

(ALP), and cholinesterase (CHE) of WT and Mac-KO mice at the end of the treatment. The data for Figure S4A are located in Table S49.

(B) Representative flow cytometry gating graphs and quantification of macrophages and neutrophils in the liver of WT or Mac-KO mice at the end of the treatment. An unusual observation (outlier) was excluded in the Mac-KO-CMC group. The data for Figure S4B are located in Table S50.

(C) Quantification of cytokines IL-10 and IL-23, IL-12p70 and IL-18 in the liver of WT or Mac-KO mice at the end of the treatment (n=5/group). The data for Figure S4C are located in Table S51.

Data are represented as mean ± SD; *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, n.s, no significance, relative to vehicle control or WT DEHP; Two-way ANOVA with Turkey's post-test.

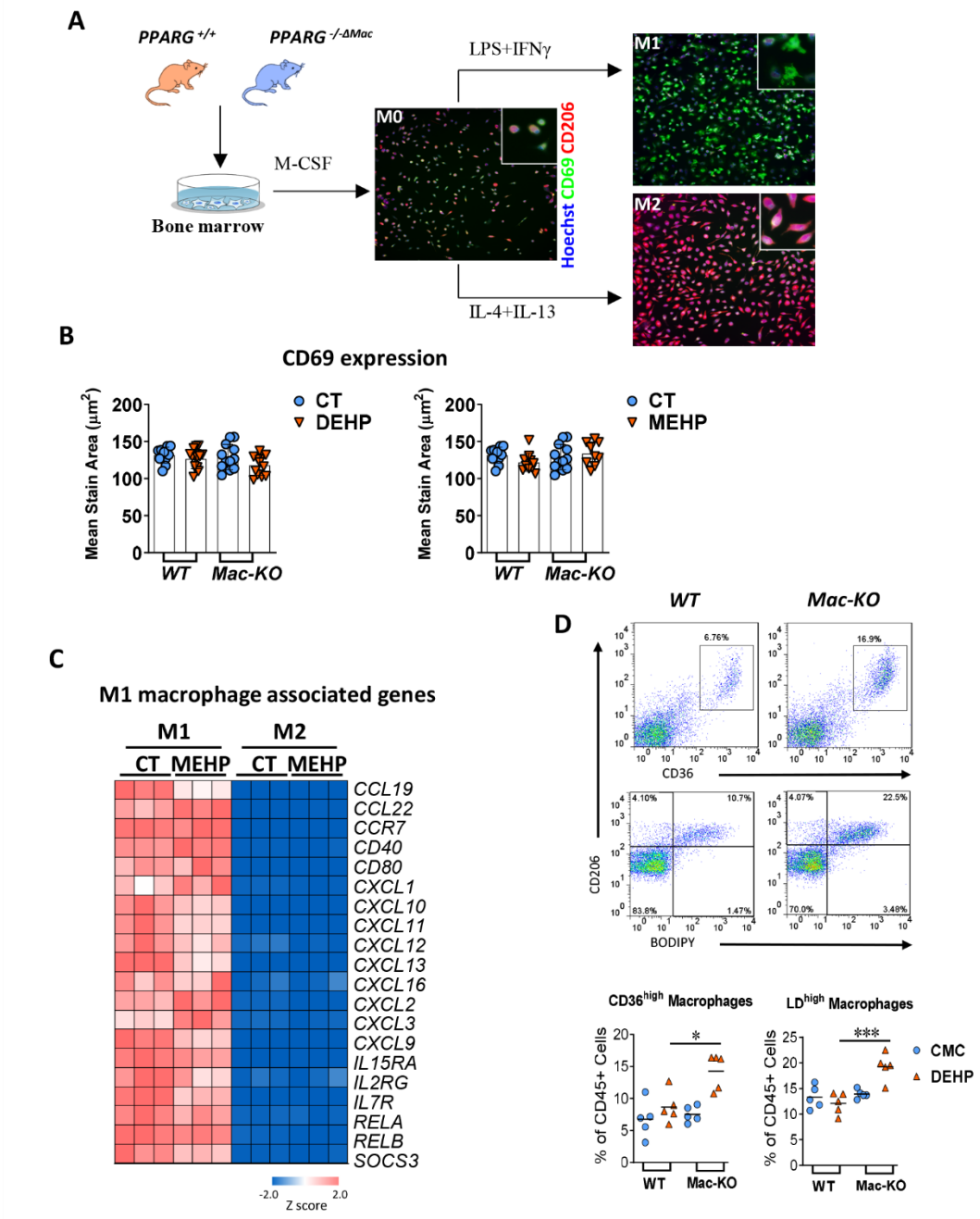


Figure S5. The effects of DEHP and MEHP on Macrophages polarization.

(A) Experimental scheme of polarization model with the bone marrow derived macrophages (BMDMs).

(B) Quantification of CD69 (M1 marker) expression in BMDMs from WT or Mac-KO mice. BMDMs were isolated from the Wild-type (WT, n=5/group) and macrophage-specific PPARγ knockout (Mac-KO, n=5/group) C57BL/6J male mice. BMDMs were

treated with 0.1% DMSO control (CT), DEHP (200 μM) or MEHP (200 μM) in combination with lipopolysaccharide (LPS, 100 ng/ml) and recombinant murine IFN-γ (50 ng/ml) for 24 h in in triplicate wells (the plots contains all technical replicates from 3-5 imaging sites of each well). Cells with positive stain of CD69 were acquired with ImageXpress system and normalized to the total cells in each of the replicate wells. The data for Figure S5B are located in Table S52.

(C) Heatmap of M1 marker genes expression in THP-1 derived macrophages. THP-1 derived M0 macrophages were treated with MEHP (200 μM) during the induction of M1 and M2 polarization. Cells from triplicate wells (n=3) were analyzed with RNA sequencing at the end of the treatment. The data for Figure S5C are located in Table S53.

(D) Representative flow cytometry gating graphs and quantification of CD36 expression and lipid droplets (LD) level in hepatic macrophages of WT and Mac-KO mice model. Wild-type (WT, n=5/group) and macrophage-specific PPARγ knockout (Mac-KO, n=5/group) C57BL/6J male mice were treated with 0.5% (wt/vol) sodium carboxymethylcellulose (CMC, vehicle control) or DEHP (625 mg/kg bw) by daily gavage for 28 days. The data for Figure S5D are located in Table S54.

Data are represented as mean ± SD; *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, n.s, no significance, relative to vehicle control or WT DEHP; Two-way ANOVA with Bonferroni's post-test.