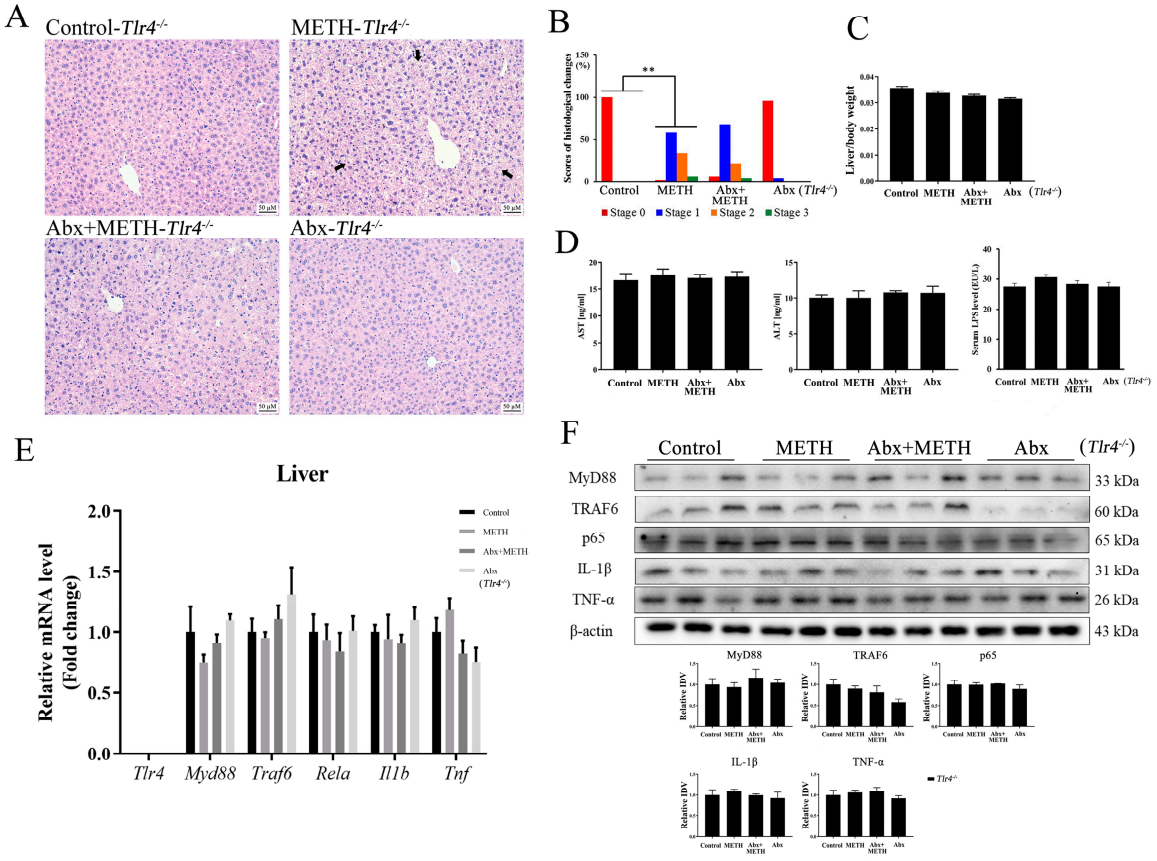
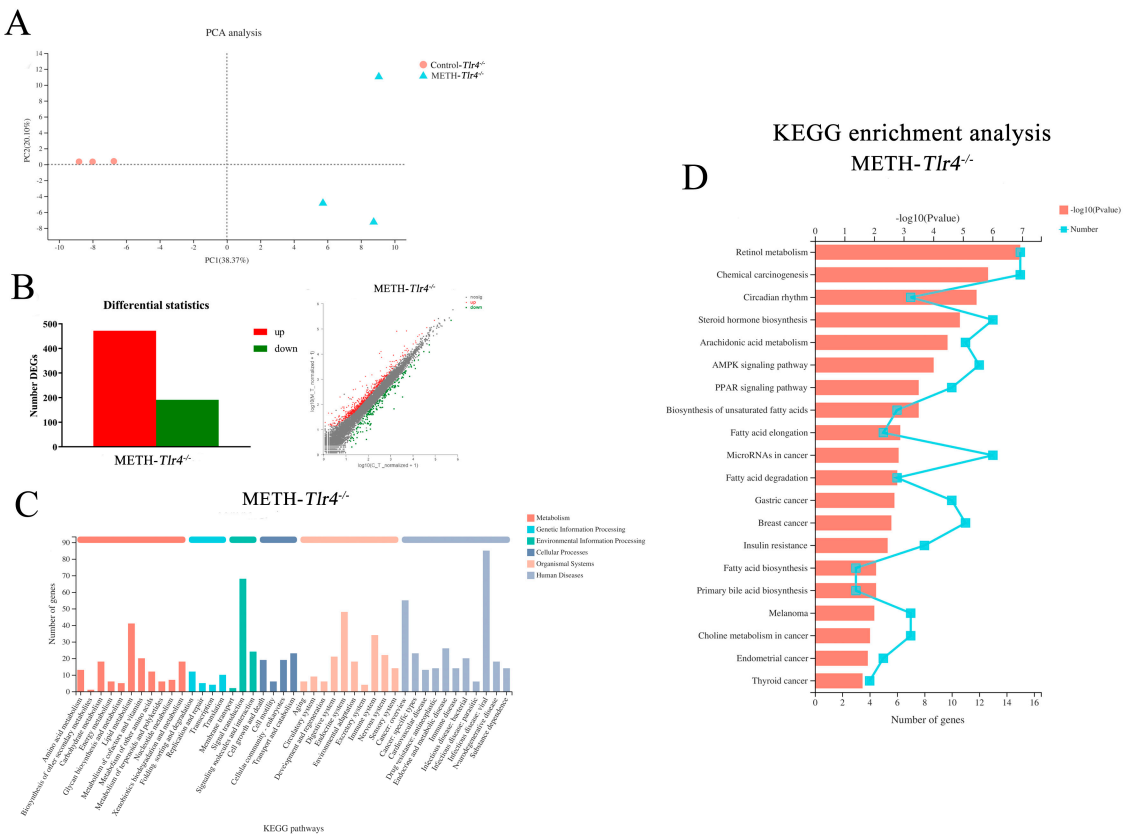


Supplementary Figure S1 The effect of METH treatment on inflammation in the livers of *Tlr4*$^{-/-}$ mice. (A) Histopathological observation. (B) The scores of histological changes. (C) The relative liver weights. (D) Effect of METH on serum AST, ALT, and LPS levels. (E) The mRNA expression of *Tlr4*, *Myd88*, *Traf6*, *Rela*, *Il1b* and *Tnf* in the mouse liver. METH had no significant effect on the expression levels of the above mRNAs across the groups. (F) Western blotting analysis of the expression of MyD88, TRAF6, p65, IL-1β, and TNF-α in mouse liver. $^{**}p < 0.01$.



Supplementary Figure S2 The results of RNA-Seq analysis in *Tlr4*$^{-/-}$ mice. (A) Principal component analysis. (B) Identification of DEGs using the histogram and scatter plot methods (|log2FC| $\geqslant$ 1, p-value < 0.05). (C) KEGG functional annotation analysis for metabolic pathways. (D) KEGG enrichment analysis in METH-treated *Tlr4*$^{-/-}$ mice.

Supplementary Table S1. Top 10 up- and down-regulated genes in METH-treated wild-type (WT) mice compared to the control group

	Gene name	Regulate	FC (M_WT/C_WT)	*P* adjust
1	*Gm45140*	up	603.3	5.42E-12
2	*E130208F15Rik*	up	542.1	4.04E-11
3	*Gm6741*	up	171.1	3.14E-06
4	*Gm15429*	up	163.8	1.67E-06
5	*Gm28177*	up	139.9	2.54E-13
6	*Gm18537*	up	124.5	1.12E-05
7	*Zfp91*	up	113.6	0.0355
8	*Chrna4*	up	91.8	4.50E-12
9	*Slc4a1*	up	89.0	0.0007
10	*Gm10131*	up	83.5	0.0003
11	*Hsd3b1*	down	-4313.3	3.23E-21
12	*Gm15832*	down	-1000.0	7.36E-06
13	*Gm47025*	down	-333.3	3.79E-09
14	*Gm44775*	down	-166.7	9.65E-06
15	*Gm20708*	down	-142.9	0.0003
16	*C330002G04Rik*	down	-111.1	6.55E-08
17	*Gm7666*	down	-111.1	0.0010
18	*Gm11537*	down	-100.0	0.0004
19	*Rps2-ps13*	down	-83.3	0.0006
20	*Gm36995*	down	-83.3	0.0006

FC, fold change

Supplementary Table S2. Top 10 up- and down-regulated genes in METH-treated *Tlr4*$^{-/-}$ mice compared to METH-treated wild-type (WT) mice

	Gene name	Regulate	FC (M_*Tlr4*$^{-/-}$/M_WT)	*P* adjust
1	*Gm28047*	up	553.3	3.57E-11
2	*Ptprn2*	up	282.1	2.54E-08
3	*Bsn*	up	244.0	9.90E-23
4	*Gm18999*	up	166.5	2.64E-06
5	*4930441H08Rik*	up	139.3	1.13E-05
6	*Moxd1*	up	136.0	3.87E-08
7	*Gm5898*	up	127.6	2.69E-08
8	*Htr1d*	up	79.7	0.0007
9	*Gm50139*	up	61.4	0.0062
10	*Gm18853*	up	54.1	0.0126
11	*Gm16867*	down	-1000.0	4.47E-12
12	*Btnl9*	down	-142.9	2.91E-06
13	*Cyp2a4*	down	-111.1	2.11E-30
14	*Gm3776*	down	-100.0	0.0005
15	*Ccdc69*	down	-90.9	5.65E-05
16	*Gm11962*	down	-76.9	0.0010
17	*Gm27177*	down	-71.4	5.91E-11
18	*Cela2a*	down	-71.4	8.09E-06
19	*Tlr4*	down	-66.7	0.0022
20	*Lncbate1*	down	-66.7	0.0031

FC, fold change

Supplementary Table S3. The DEGs enriched in the Inflammatory mediator regulation of TRP channels and Toll-like receptor signaling pathway in METH-treated *Tlr4*$^{-/-}$ mice compared to METH-treated wild-type (WT) mice

	Gene name	Regulate	FC (M_*Tlr4*$^{-/-}$/M_WT)	*P* adjust
Inflammatory mediator regulation of TRP channels	*Cyp2c55*	down	-3.2	2.19E-05
	Camk2b	down	-5.2	3.74E-19
	Cyp4a10	down	-3.6	6.16E-05
	Cyp2c69	down	-24.5	8.20E-06
	Cyp2c38	down	-4.4	4.14E-19
	Cyp4a14	down	-9.1	9.90E-23
	Cyp4a31	down	-9.3	2.68E-17
	Cyp2c40	down	-9.5	1.56E-23
Toll-like receptor signaling pathway	*Tlr4*	down	-66.7	0.0022
	Tlr12	down	-15.9	2.18E-19
	Tlr5	down	-1.9	0.0719

FC, fold change