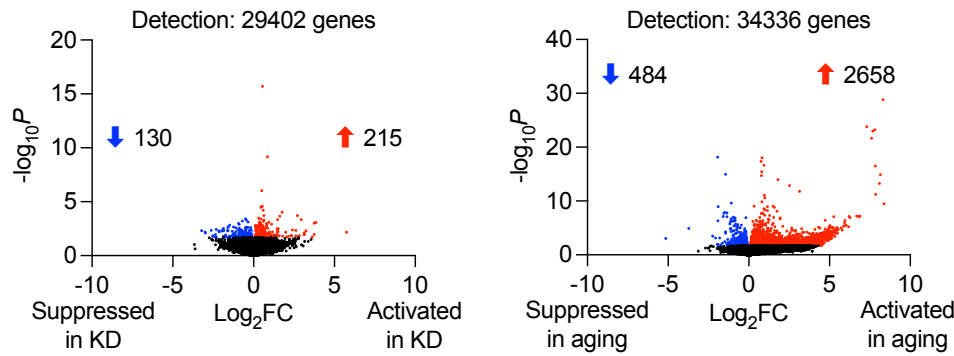
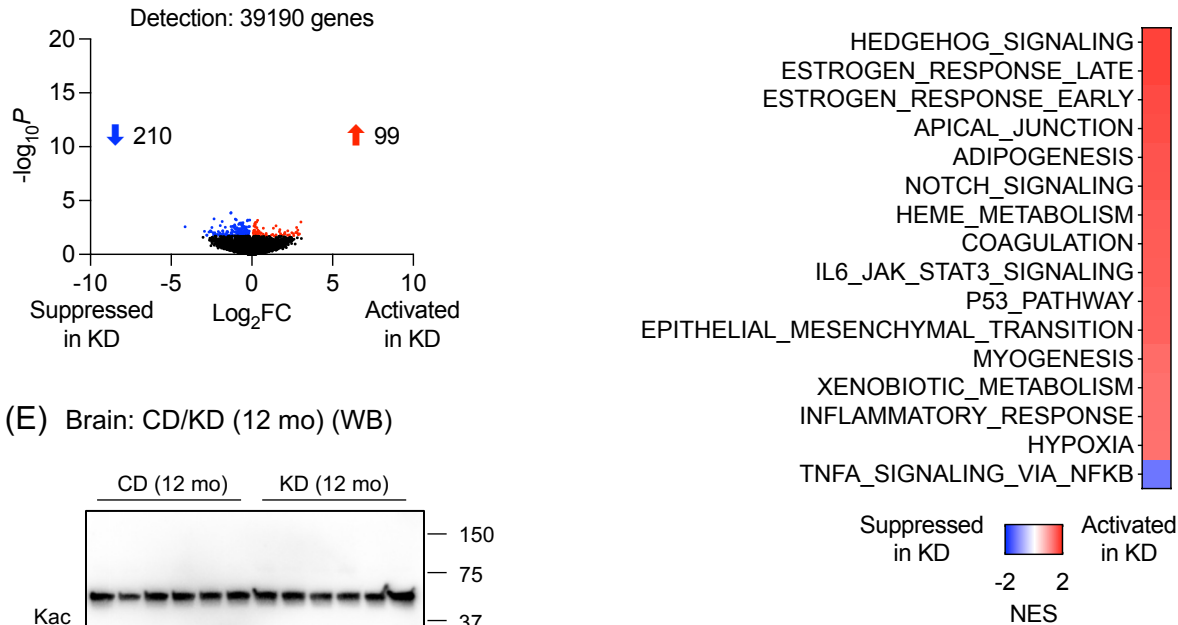


Supplemental Figure 1, related to Figure 1

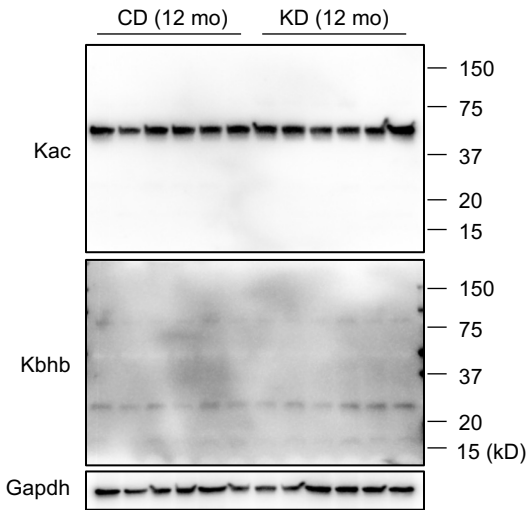
(A) Brain: KD (12 mo) vs CD (12 mo)      (B) Brain: CD (26 mo) vs CD (12 mo)



(C) Brain: Cyclic KD (26 mo) vs CD (26 mo)      (D) Brain: KD (12 mo) vs CD (12 mo) (MSigDB)

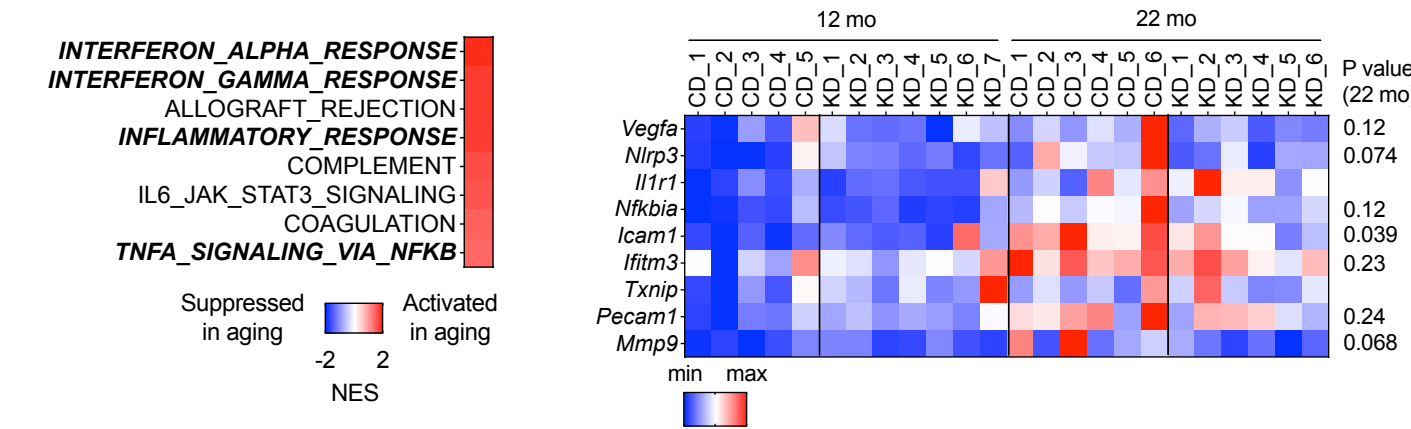


(E) Brain: CD/KD (12 mo) (WB)



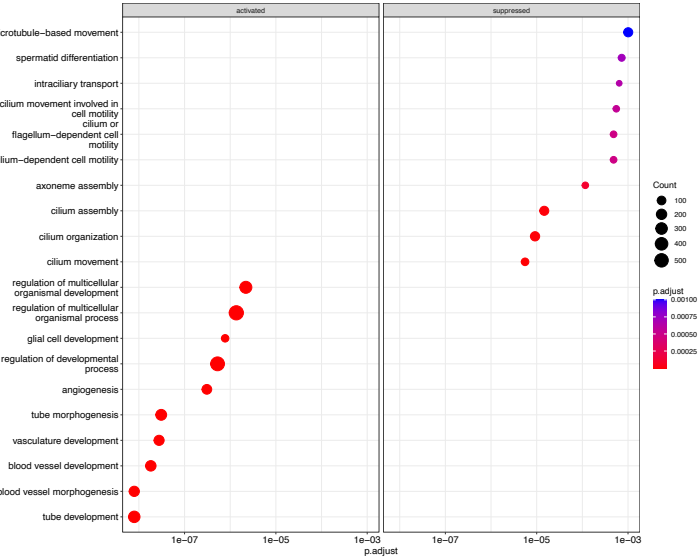
Supplemental Figure 2, related to Figure 1

(A) Brain: CD (26 mo) vs CD (12 mo) (MSigDB)(C) Brain: 1 week CD/KD (12 mo) and 1 week CD/KD (22 mo) (qPCR)

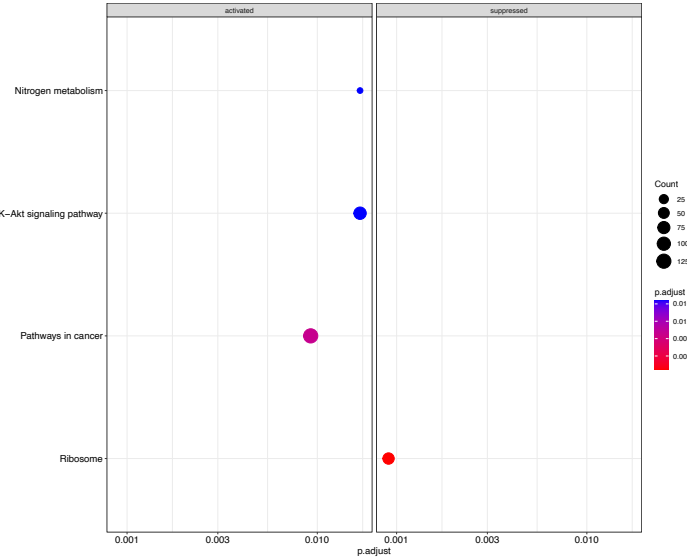


# Supplemental Figure 3, related to Figure 1

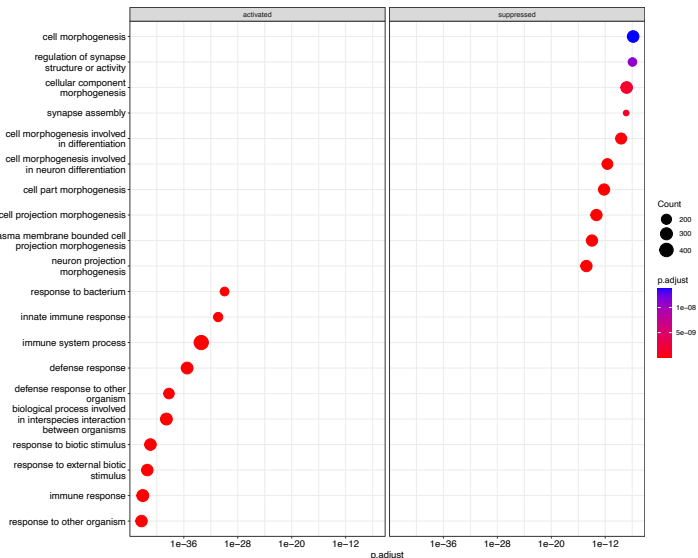
(A) Brain: KD (12 mo) vs CD (12 mo) (GO)



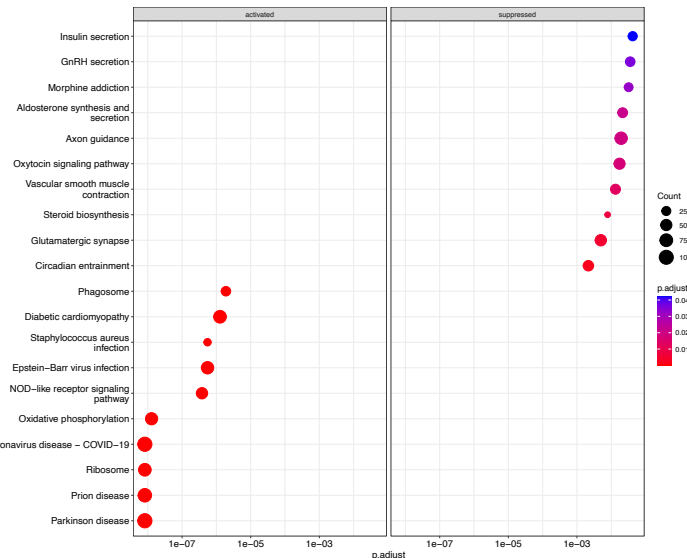
(D) Brain: KD (12 mo) vs CD (12 mo) (KEGG)



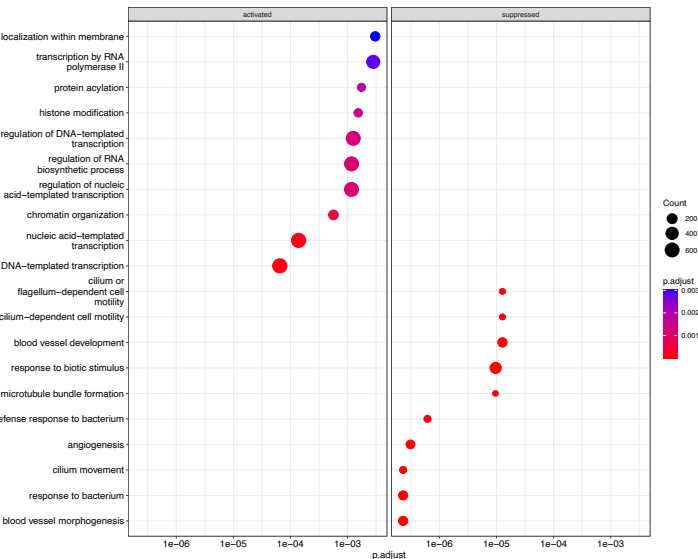
(B) Brain: CD (26 mo) vs CD (12 mo) (GO)



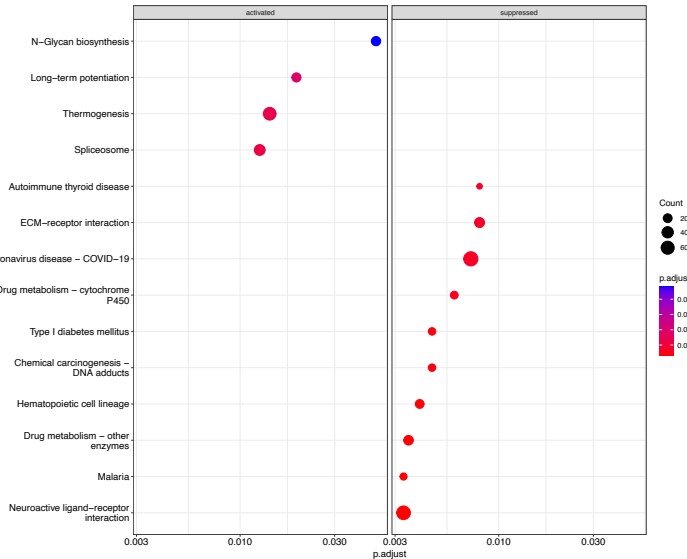
(E) Brain: CD (26 mo) vs CD (12 mo) (KEGG)



(C) Brain: Cyclic KD (26 mo) vs CD (26 mo) (GO)

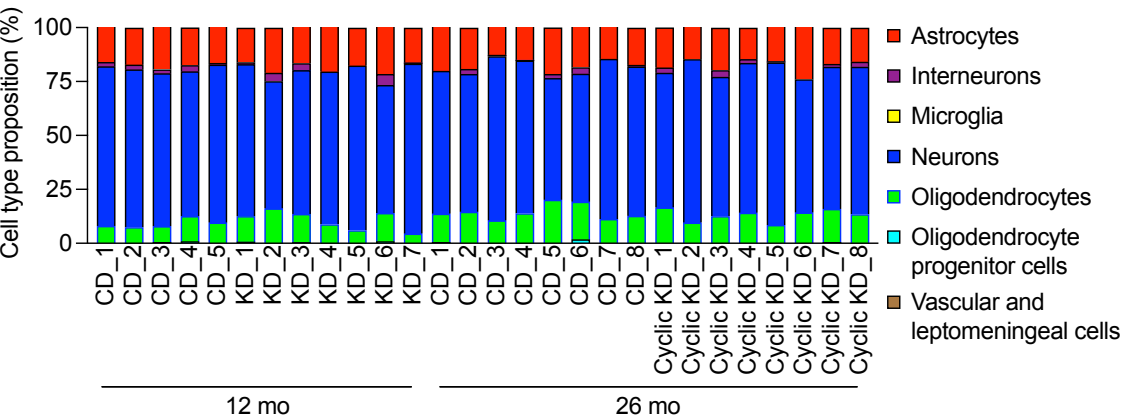


(F) Brain: Cyclic KD (26 mo) vs CD (26 mo) (KEGG)



# Supplemental Figure 4, related to Figure 1

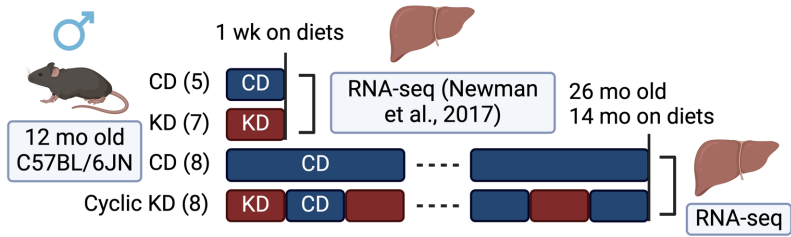
(A) Brain: CD/KD (12 mo) and CD/Cyclic KD (26 mo) (deconvolution)



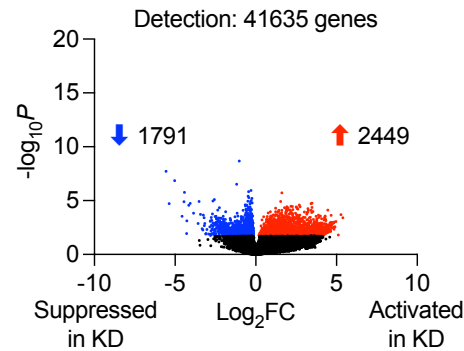


Supplemental Figure 5, related to Figure 1

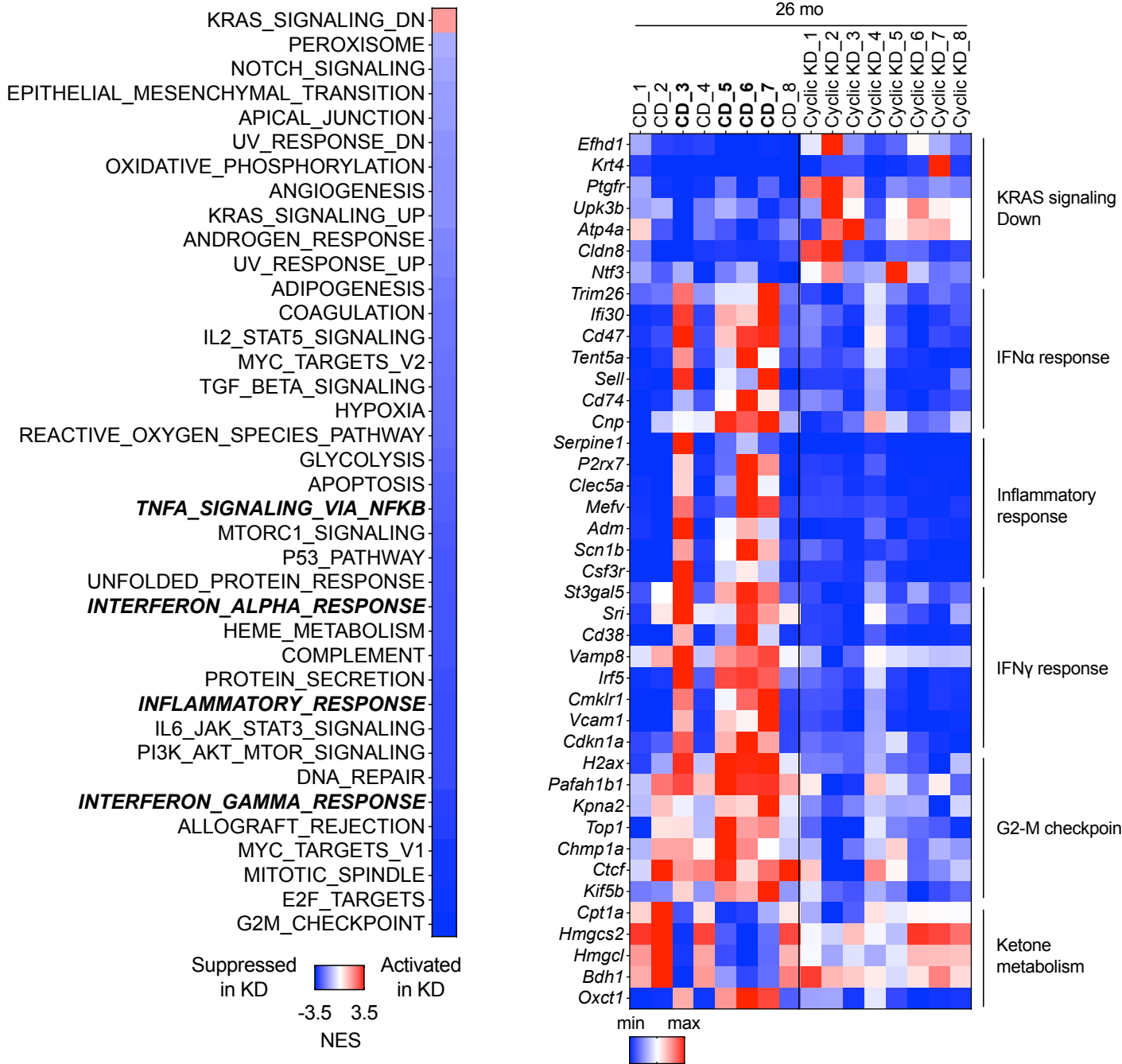
(A)



(B) Liver : Cyclic KD (26 mo) vs CD (26 mo)

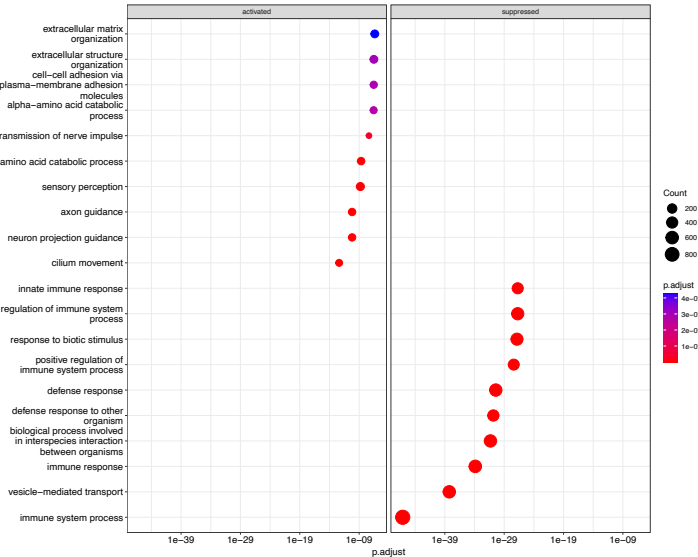


(C) Liver: Cyclic KD (26 mo) vs CD (26 mo) (MSigDB) (D) Liver: CD/Cyclic KD (26 mo) (RNA-seq)

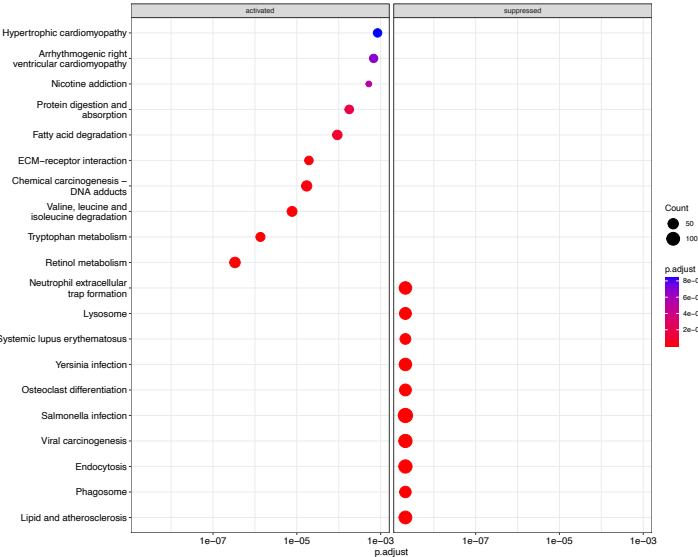


Supplemental Figure 6, related to Figure 1

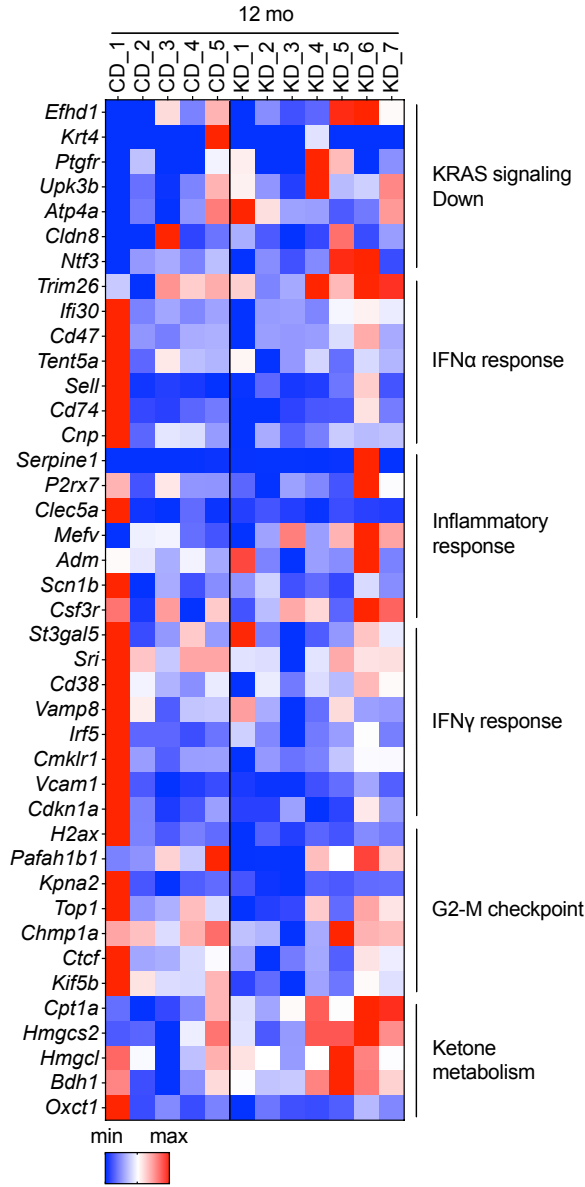
(A) Liver: Cyclic KD (26 mo) vs CD (26 mo) (GO)



(B) Liver: Cyclic KD (26 mo) vs CD (26 mo) (KEGG)



(C) Liver: CD/KD (12 mo) (RNA-seq)

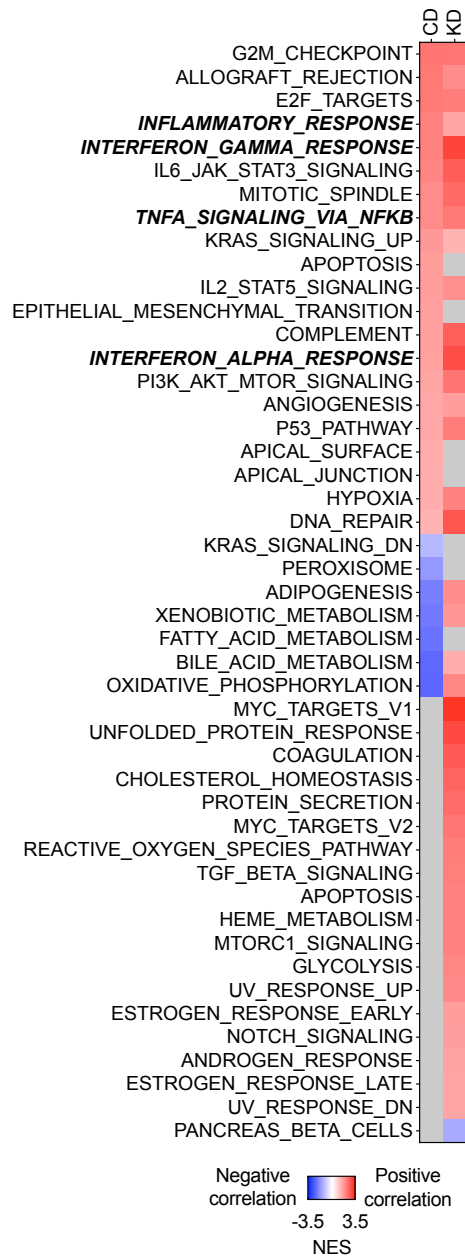


Supplemental Figure 7, related to Figure 1

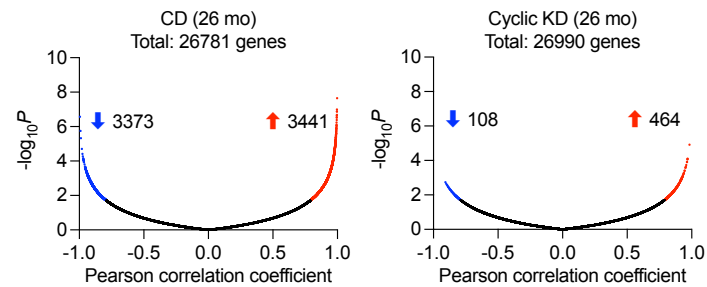
(A) CD/Cyclic KD (26 mo)

	Body (g)	Liver (g)		Body (g)	Liver (g)
CD 1	27.4	1.04	Cyclic KD 1	28.3	1.24
CD 2	32.2	1.12	Cyclic KD 2	28.3	1.32
CD 3	37.4	5.18	Cyclic KD 3	31.3	1.25
CD 4	34.2	1.42	Cyclic KD 4	27.5	1.87
CD 5	34	4.59	Cyclic KD 5	37.8	2.28
CD 6	40.8	7.77	Cyclic KD 6	31.4	1.33
CD 7	34.1	3.54	Cyclic KD 7	32.7	1.36
CD 8	32.5	1.32	Cyclic KD 8	32.6	1.55
average	34.075	3.2475	average	31.238	1.525
SD	3.907	2.4649	SD	3.3449	0.3691
		t-test		0.141	0.0709

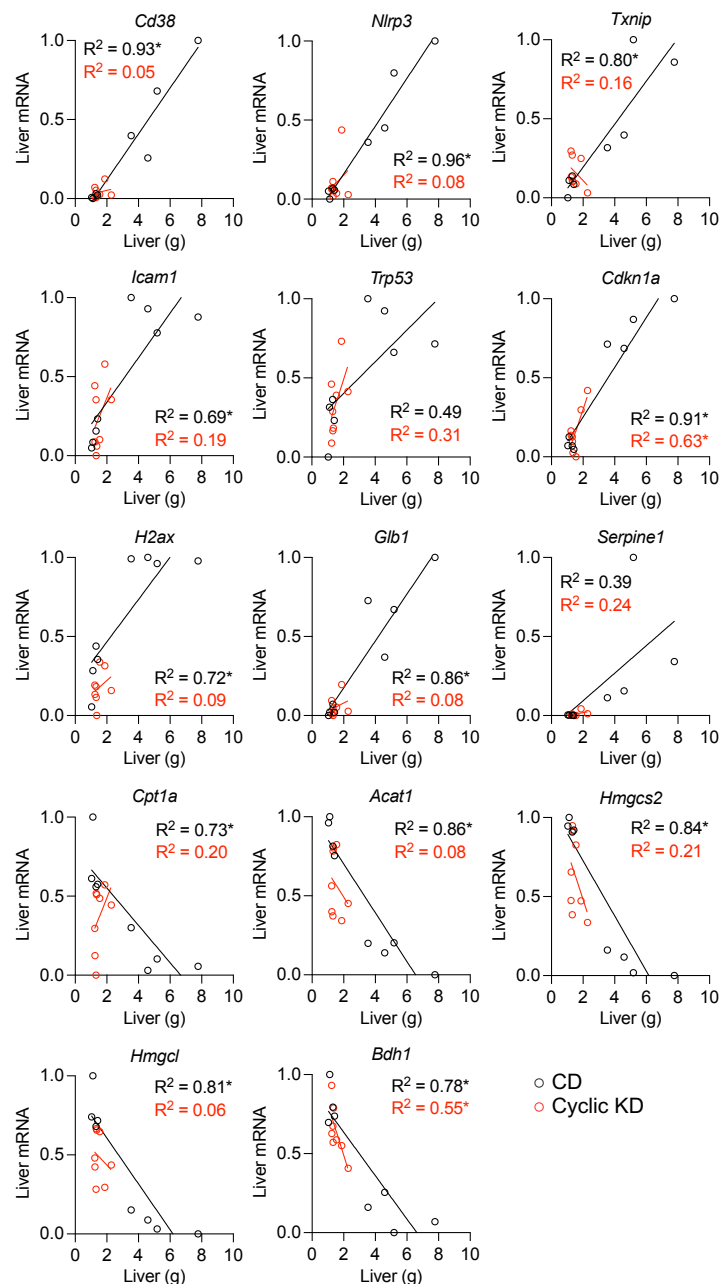
(C) Liver weight vs liver gene expression  
CD/Cyclic KD (26 mo) (MSigDB)



(B) Liver weight vs liver gene expression

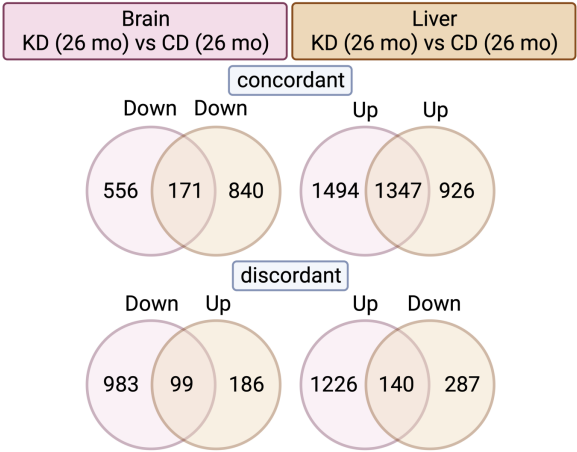


(D) Liver weight vs liver gene expression  
CD/Cyclic KD (26 mo)

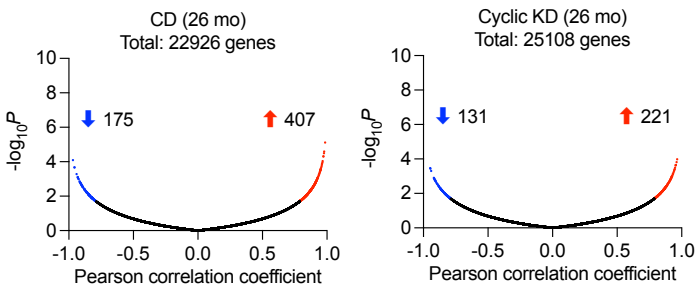


Supplemental Figure 8, related to Figure 1

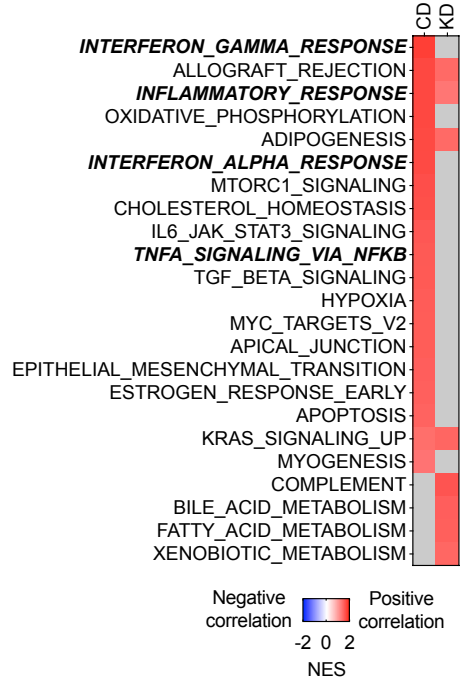
(A) Cyclic KD (brain vs liver) (RRHO)



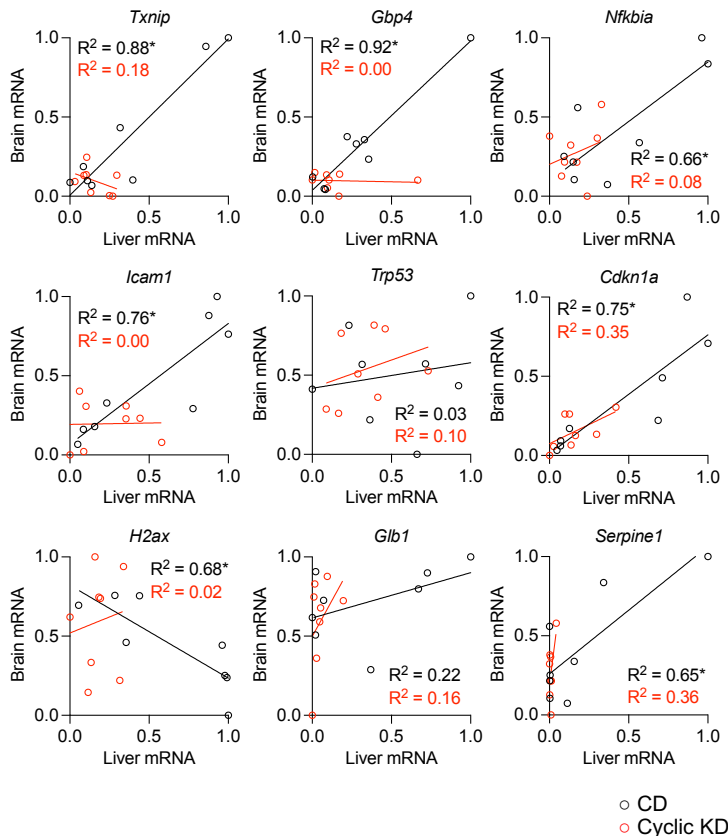
(B) Liver gene expression vs brain gene expression



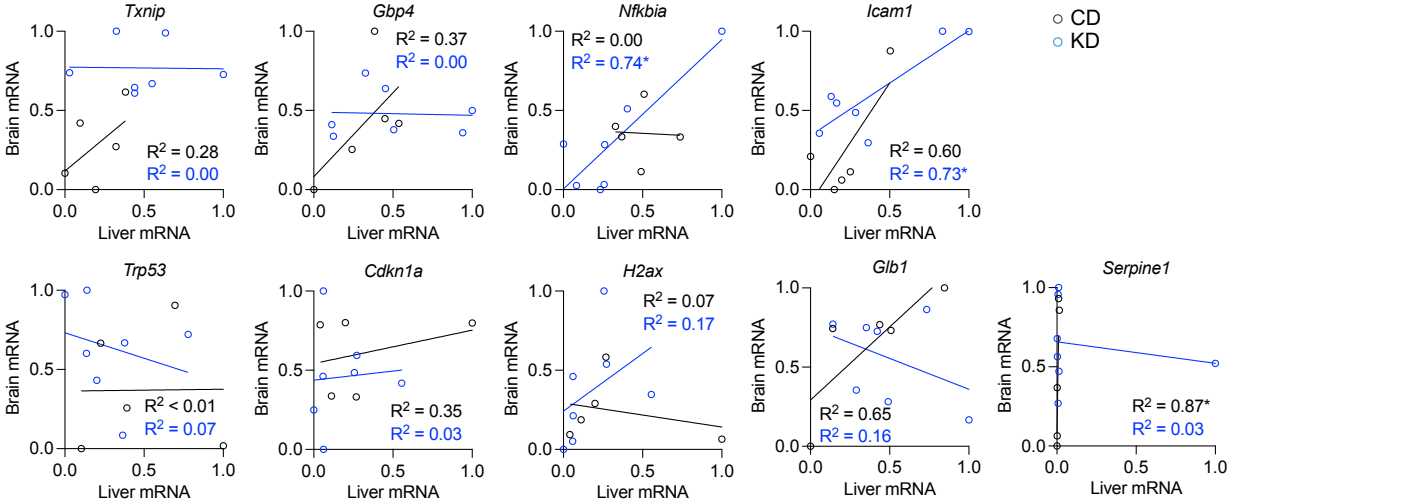
(C) Liver gene expression vs brain gene expression CD/Cyclic KD (26 mo) (MSigDB)



(D) Liver gene expression vs brain gene expression CD/Cyclic KD (26 mo)

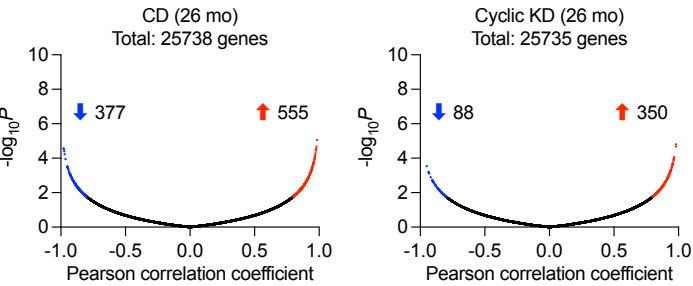


E Liver gene expression vs brain gene expression CD/KD (12 mo)

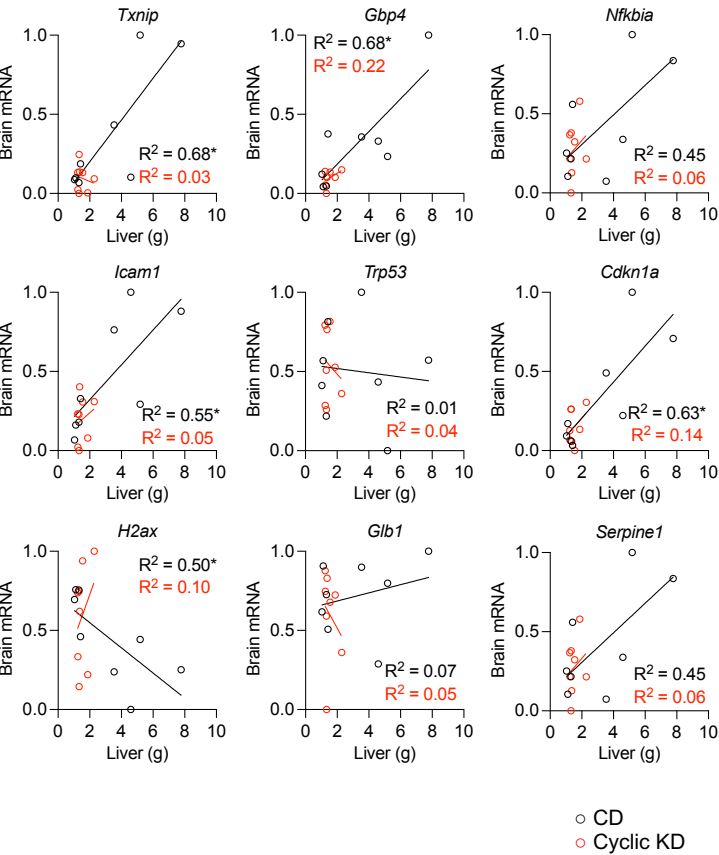


Supplemental Figure 9, related to Figure 1

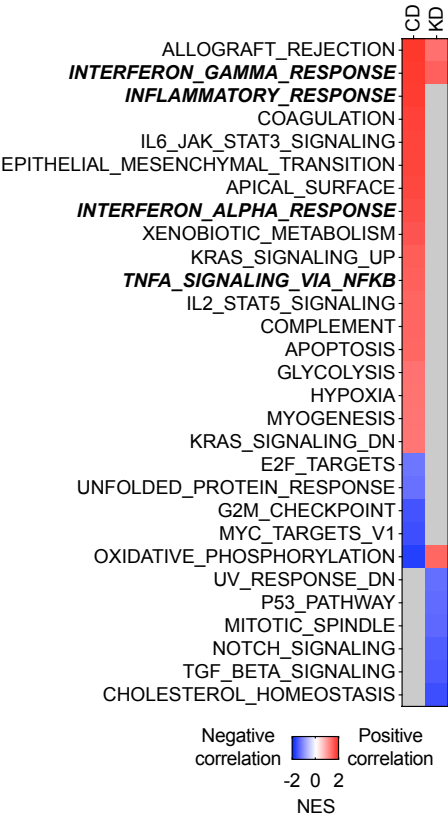
(A) Liver weight vs brain gene expression



(C) Liver weight vs brain gene expression  
CD/Cyclic KD (26 mo)

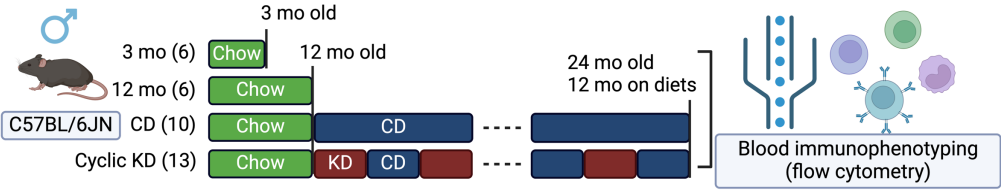


(B) Liver weight vs brain gene expression  
CD/Cyclic KD (26 mo) (MSigDB)

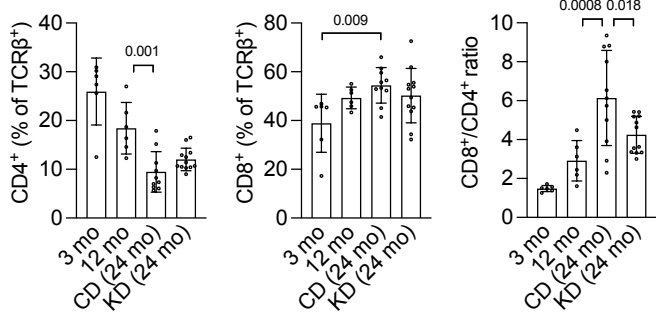


Supplemental Figure 10, related to Figure 1

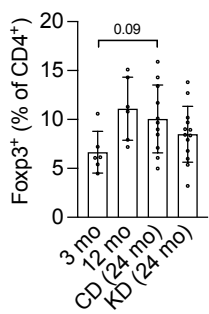
(A)



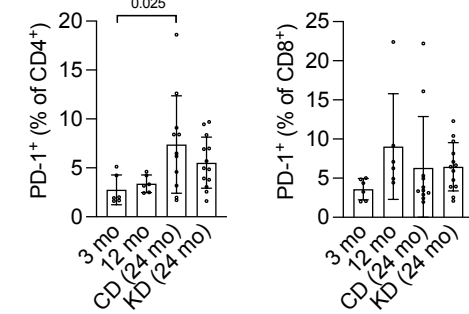
(B)



(C)

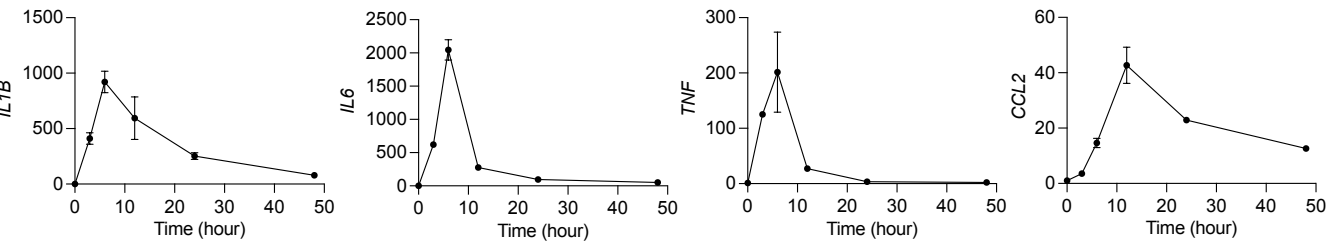


(D)

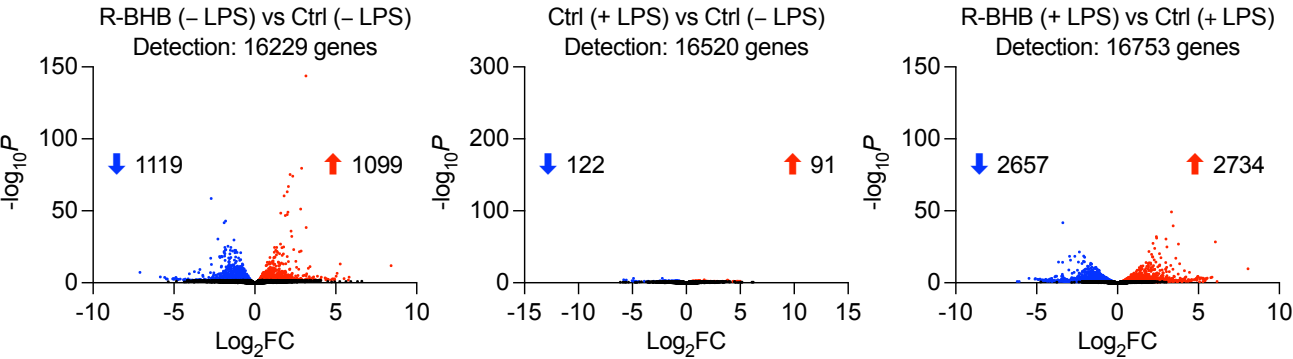


# Supplemental Figure 11, related to Figure 2

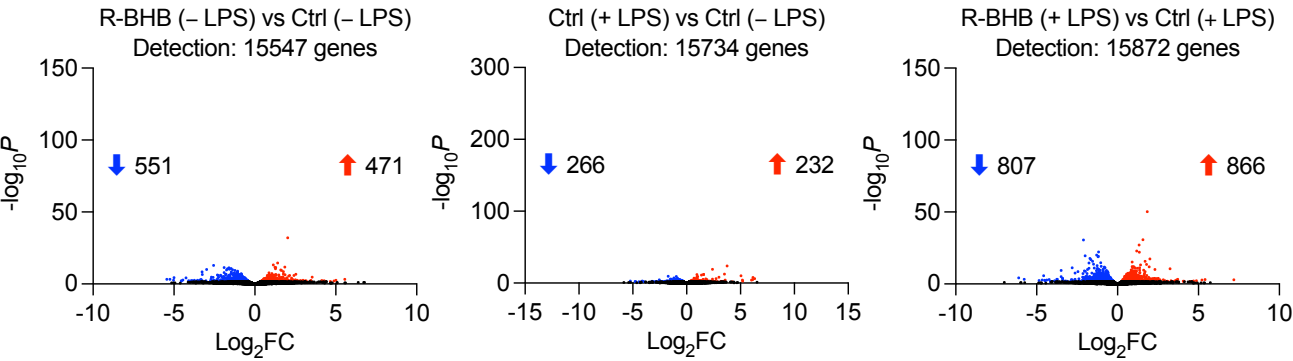
## (A) Human primary microglia (LPS time course) (qPCR)



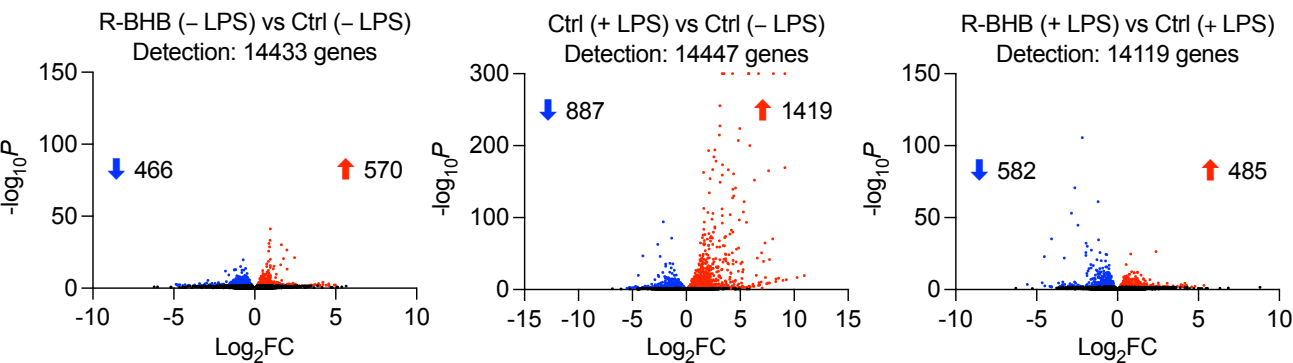
## (B) Human primary neurons



## (C) Human primary astrocytes

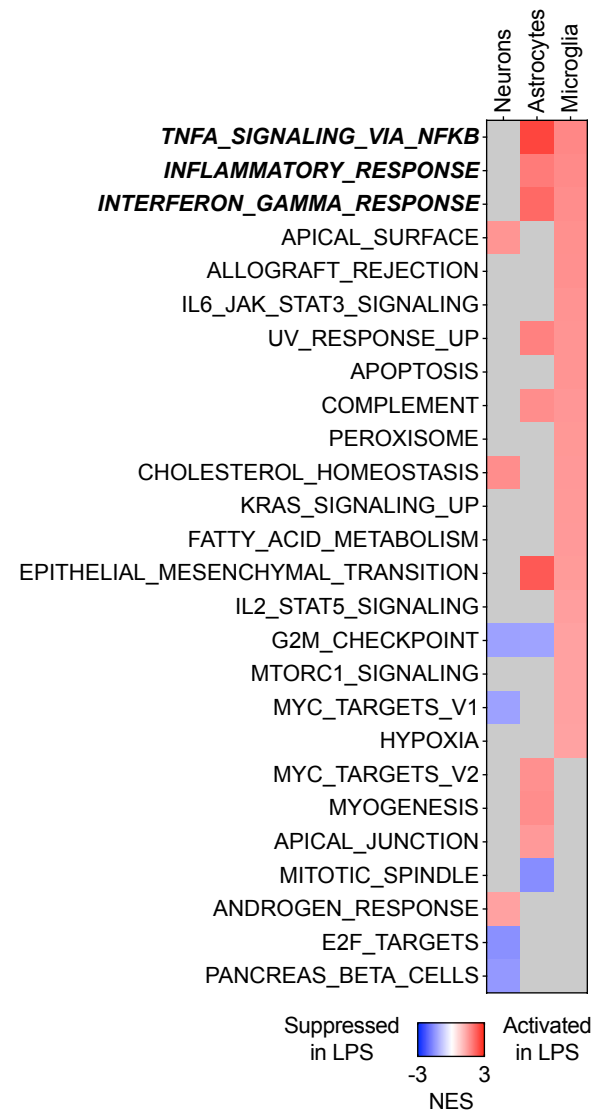


## (D) Human primary microglia

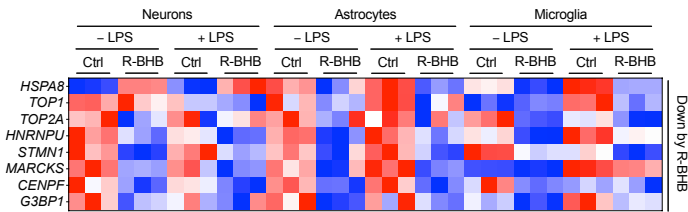


Supplemental Figure 12, related to Figure 2

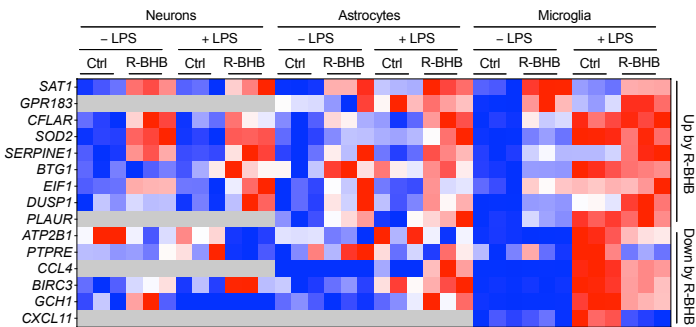
(A) Ctrl (+ LPS) vs Ctrl (– LPS) (MSigDB)



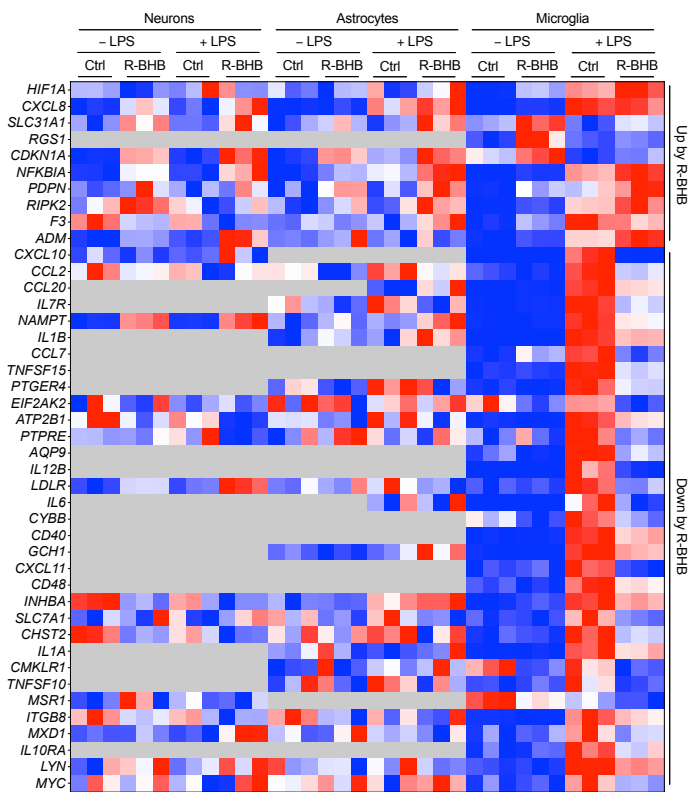
(B) G2-M checkpoint



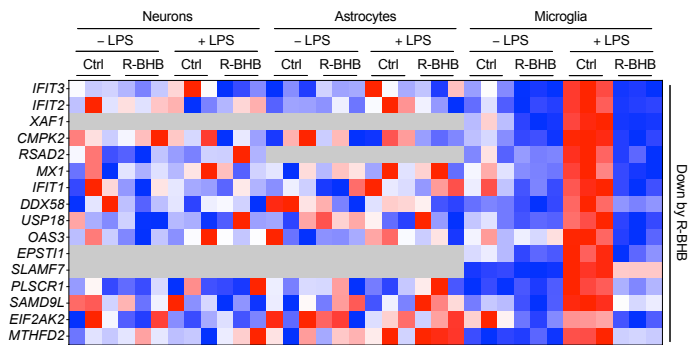
(C) TNFα signaling via NFκB



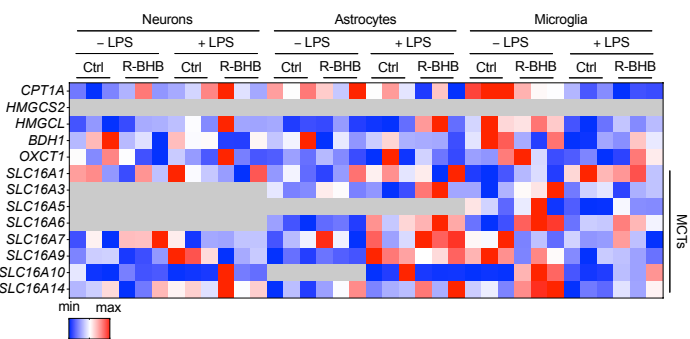
(D) Inflammatory response



(E) IFNγ response



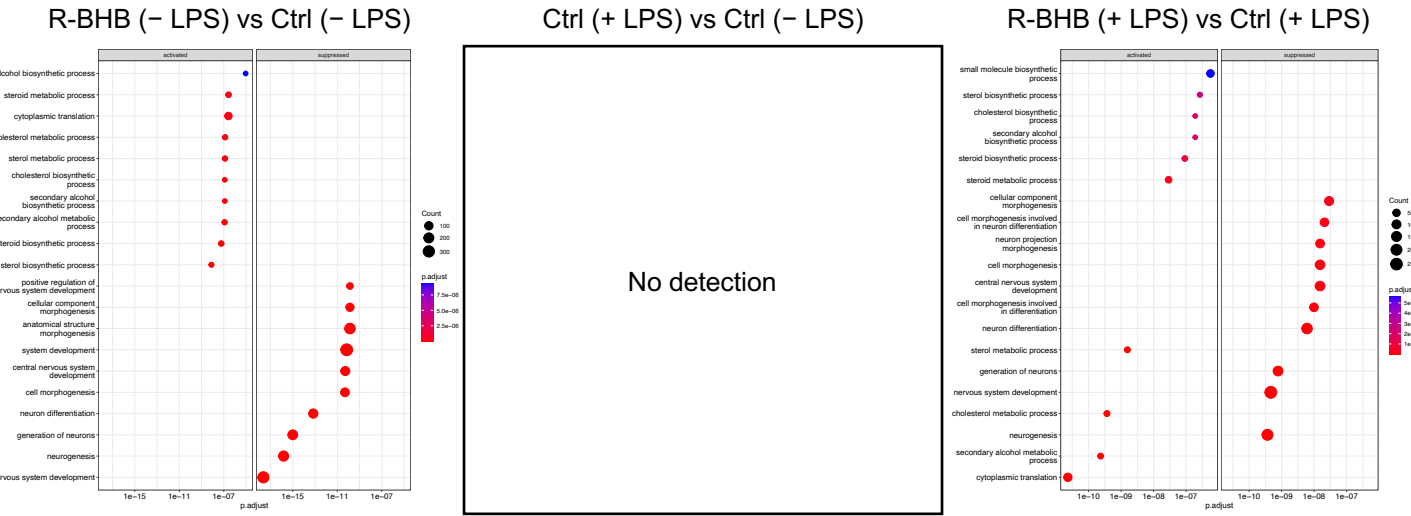
(F) Ketone metabolism



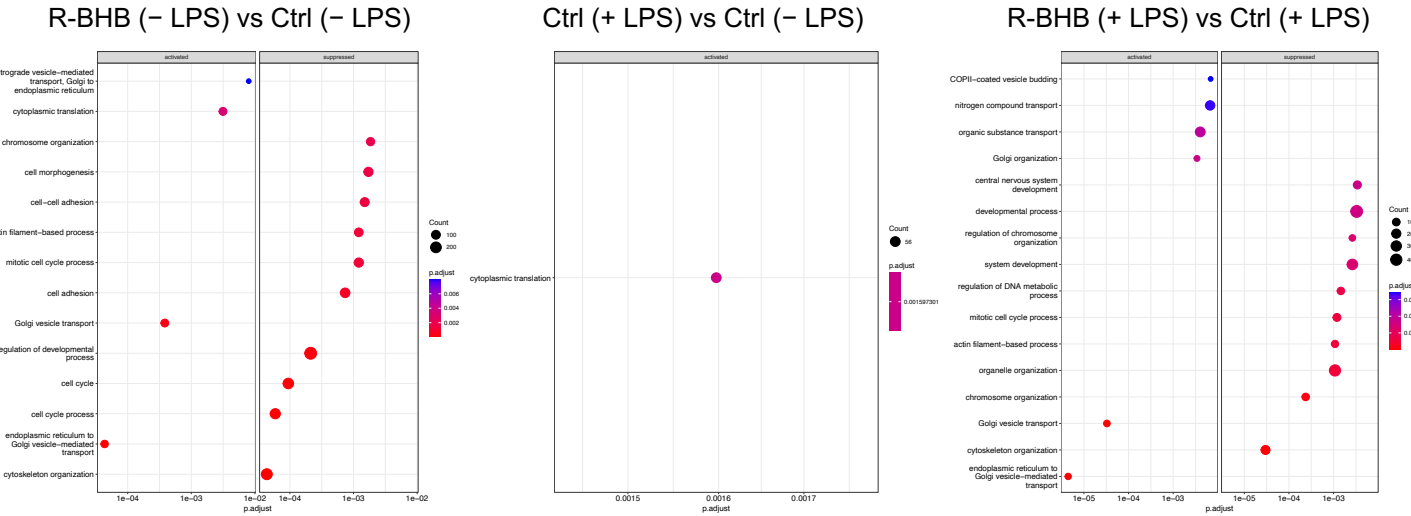


Supplemental Figure 13, related to Figure 2

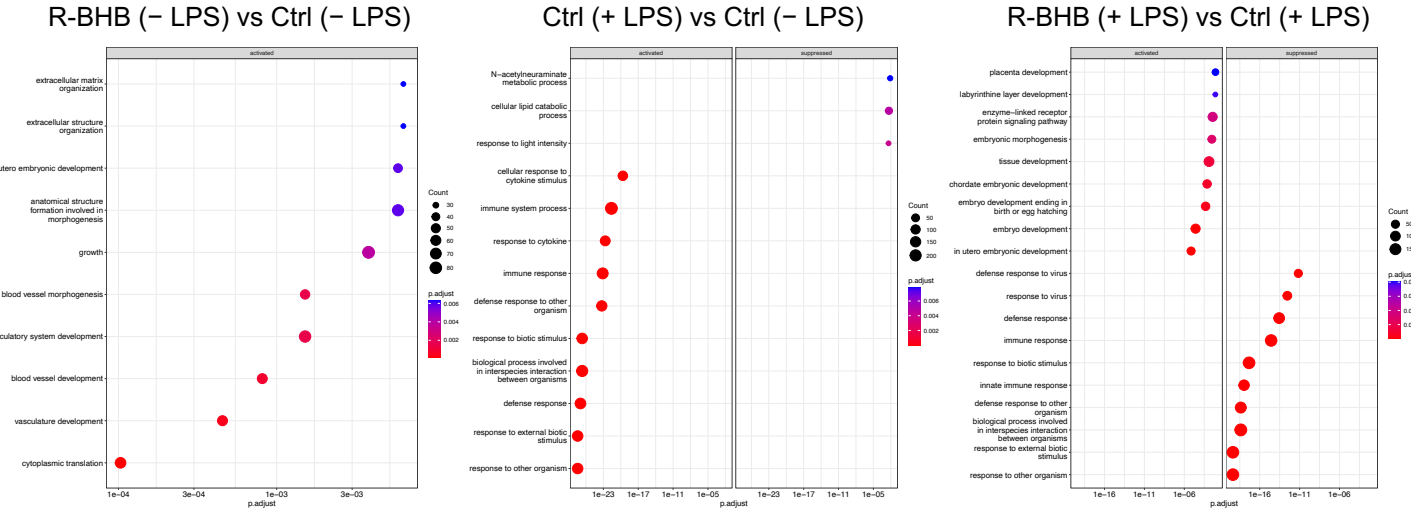
(A) Human primary neurons (GO)



(B) Human primary astrocytes (GO)

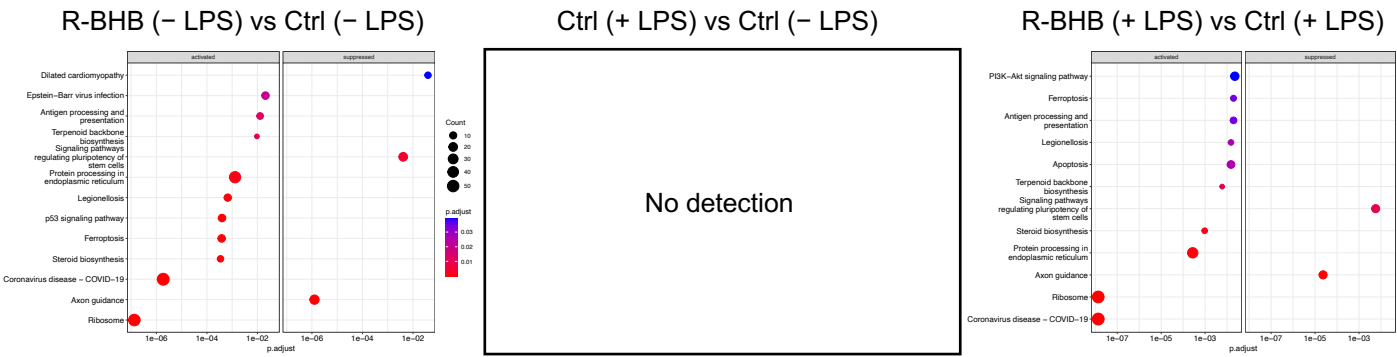


(C) Human primary microglia (GO)

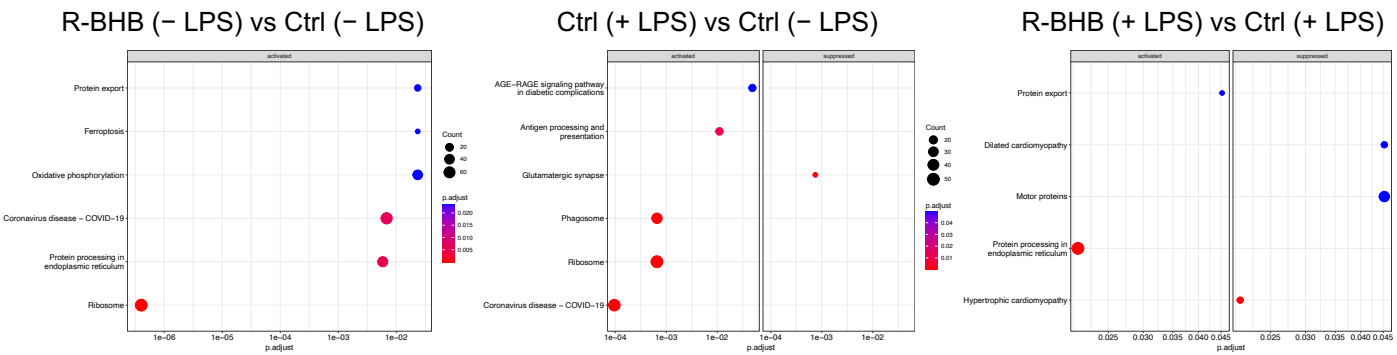


Supplemental Figure 14, related to Figure 2

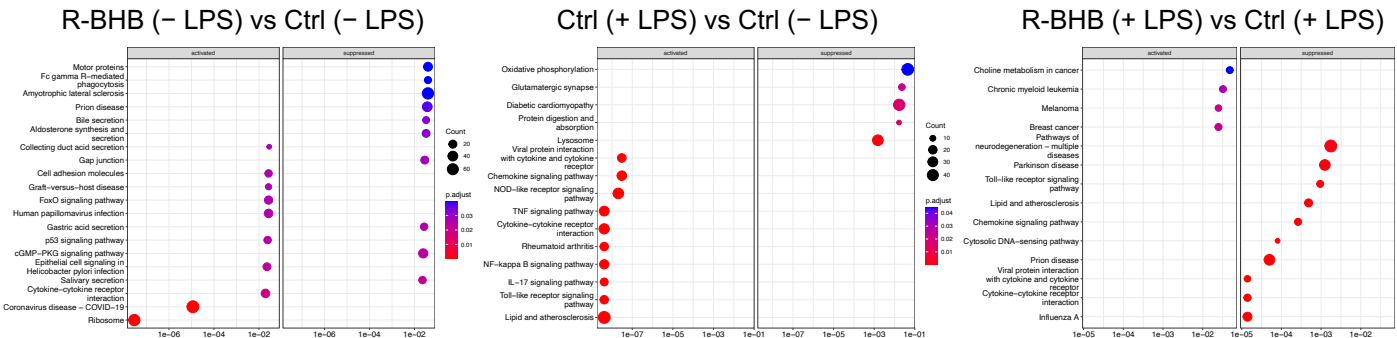
(A) Human primary neurons (KEGG)



(B) Human primary astrocytes (KEGG)

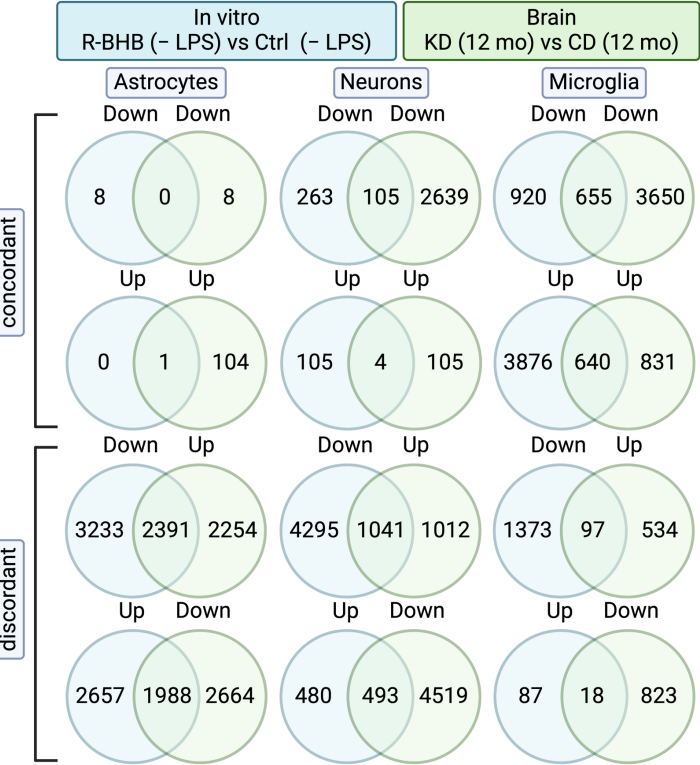


(C) Human primary microglia (KEGG)

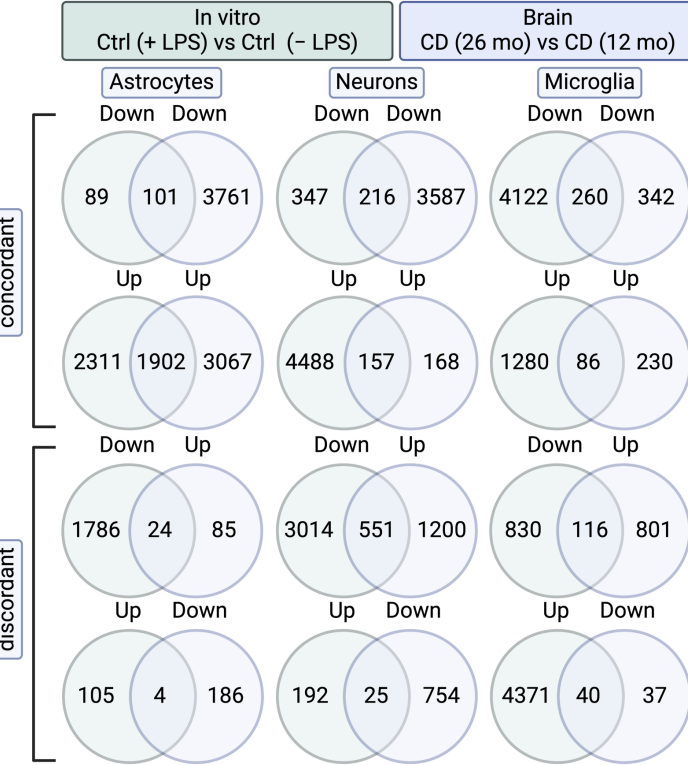


Supplemental Figure 15, related to Figure 2

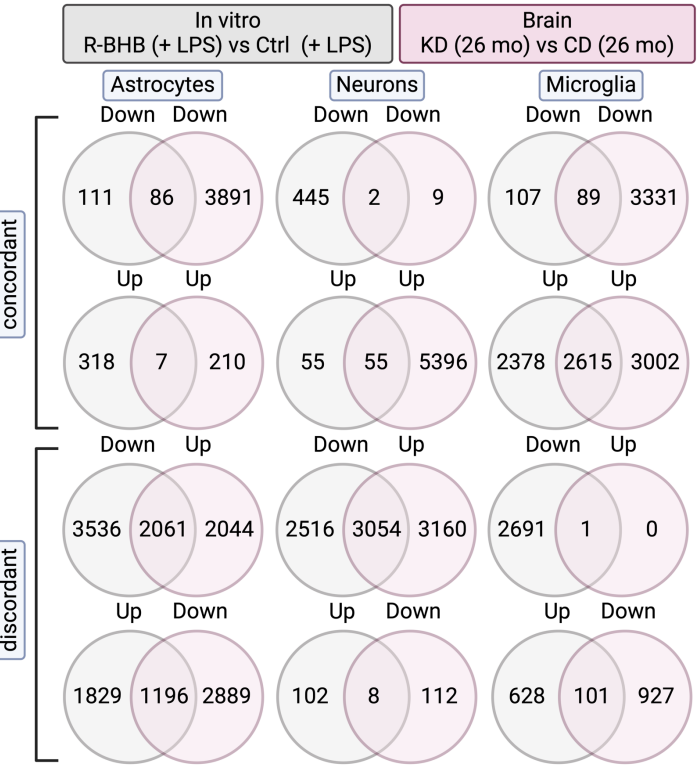
(A) Brain cells (R-BHB) vs Brain (KD) (RRHO)



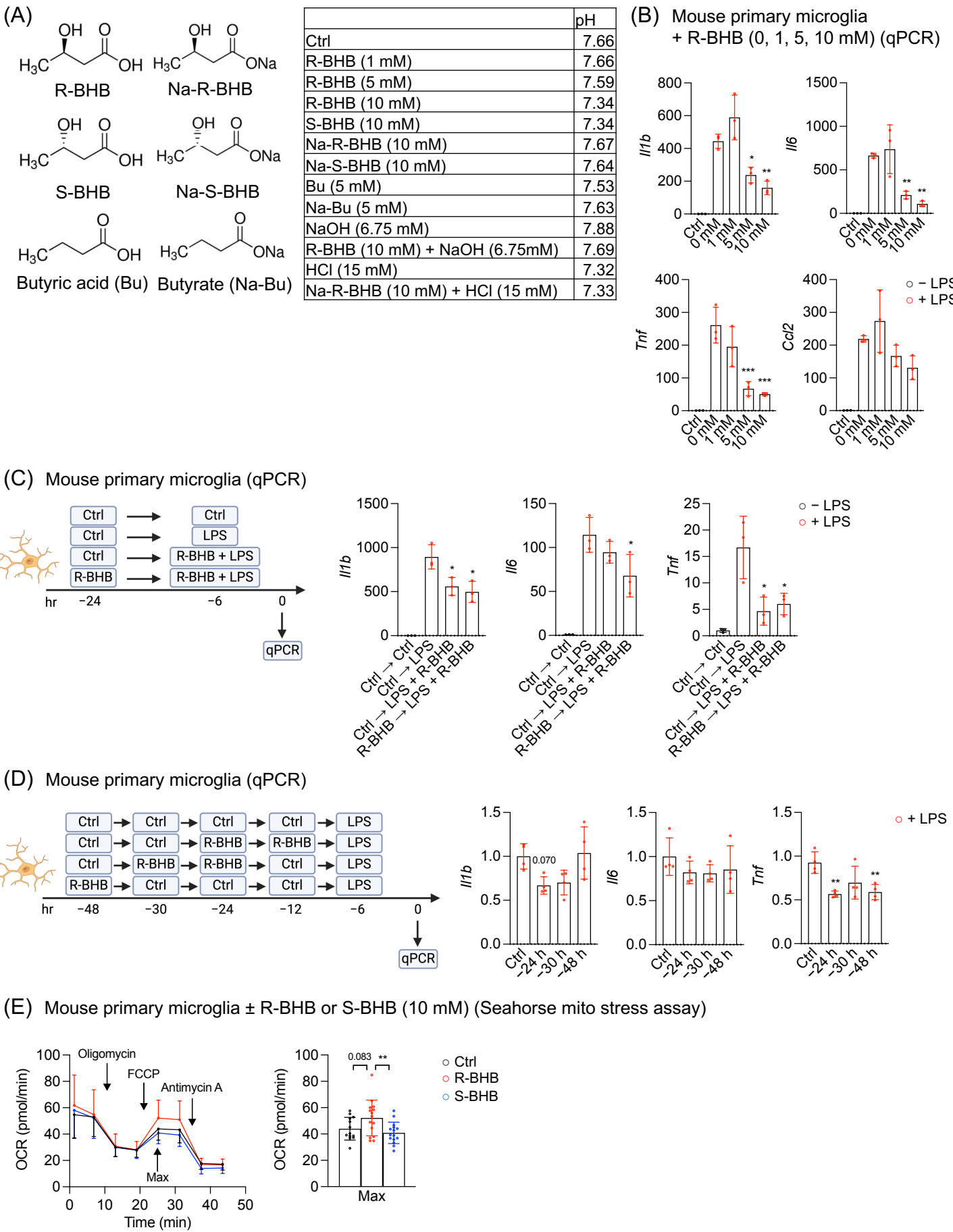
(B) Brain cells (LPS) vs Brain (aging) (RRHO)



(C) Brain cells (R-BHB + LPS) vs Brain (Cyclic KD) (RRHO)

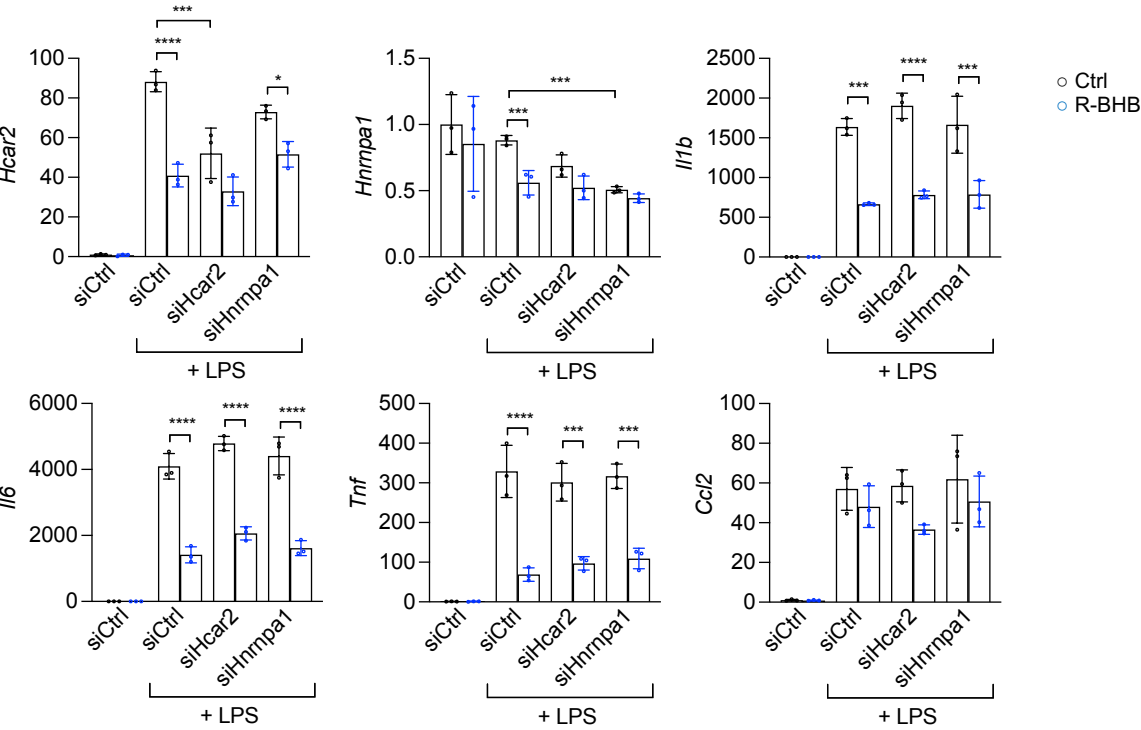


Supplemental Figure 16, related to Figure 3



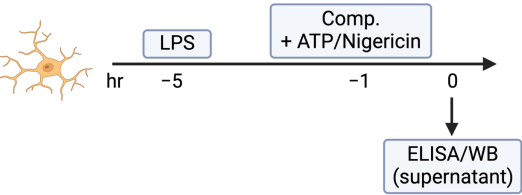
Supplemental Figure 17, related to Figure 3

(A) Mouse primary microglia ± R-BHB (10 mM) ± siHcar2 ± siHnrpa1 (qPCR)

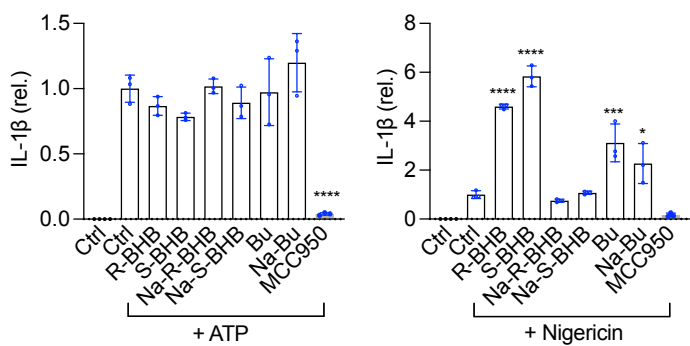


Supplemental Figure 18, related to Figure 3

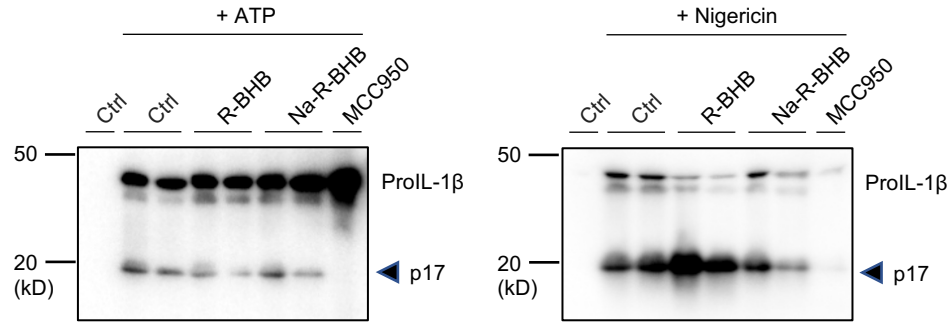
(A)



(B) Mouse primary microglia (ELISA)

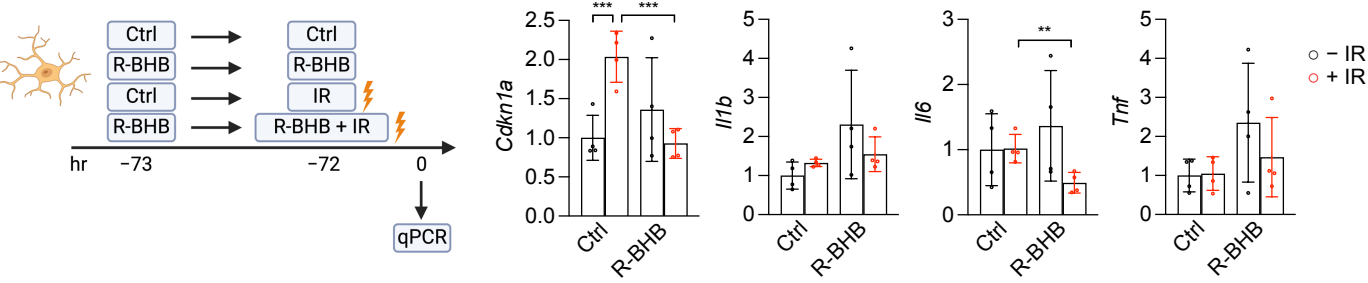


(C) Mouse primary microglia (WB)

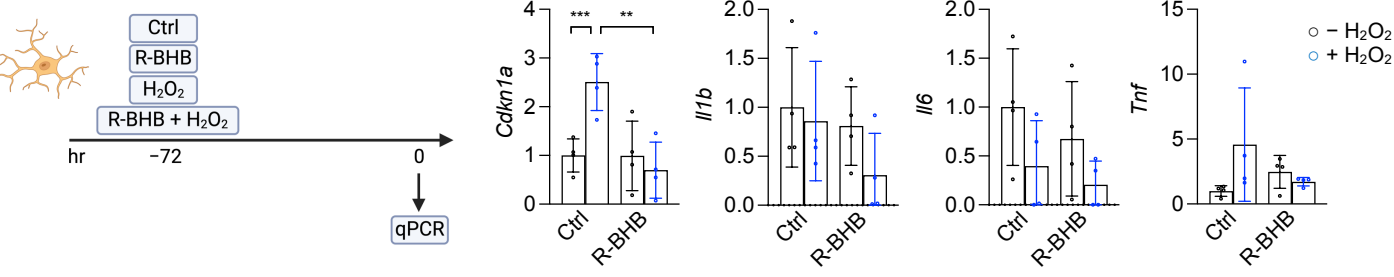


Supplemental Figure 19, related to Figure 3

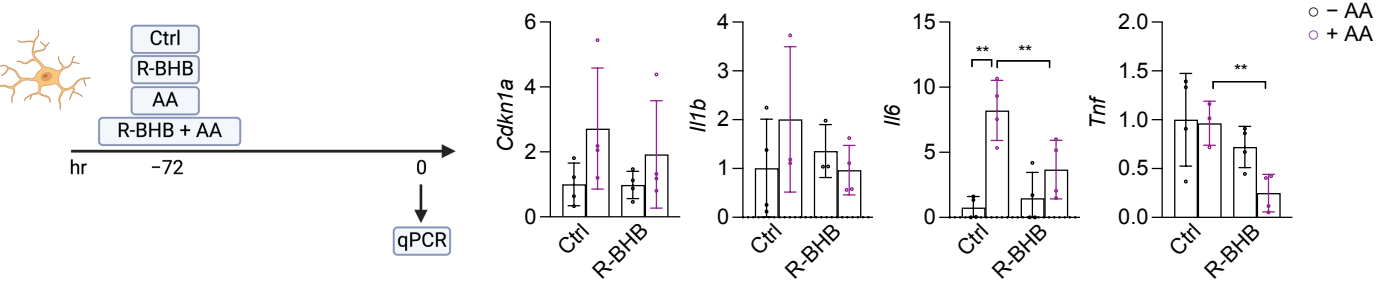
(A) Mouse primary microglia ± R-BHB (10 mM) ± IR (15 Gy) (qPCR)



(B) Mouse primary microglia ± R-BHB (10 mM) ± H<sub>2</sub>O<sub>2</sub> (150 μM) (qPCR)

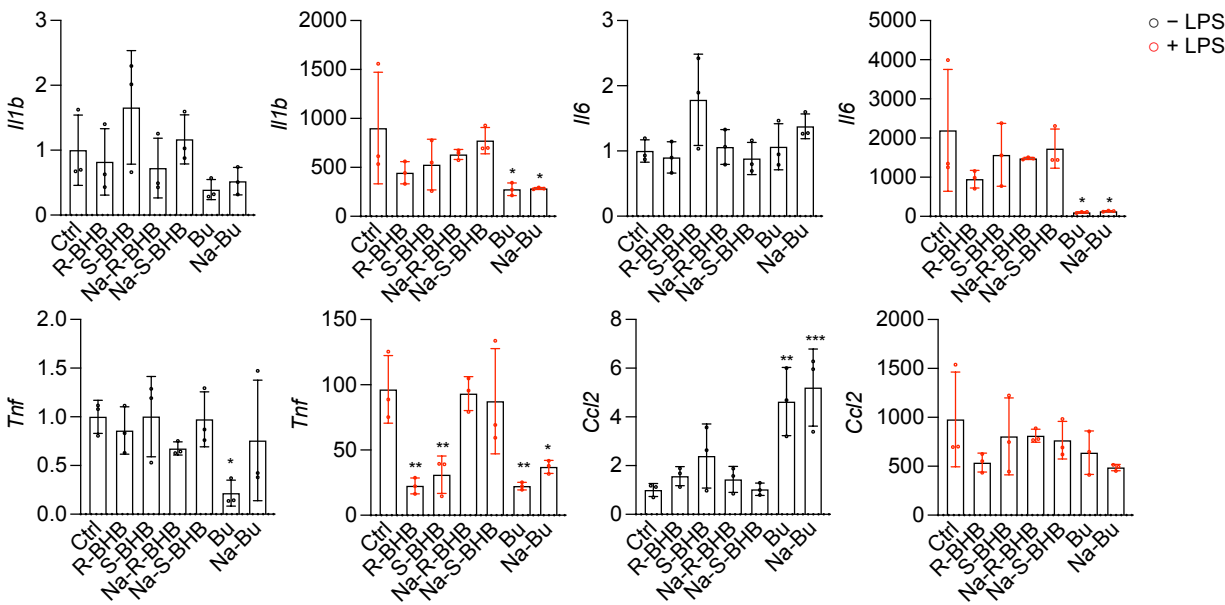


(C) Mouse primary microglia ± R-BHB (10 mM) ± arachidonic acid (AA) (300 μM) (qPCR)

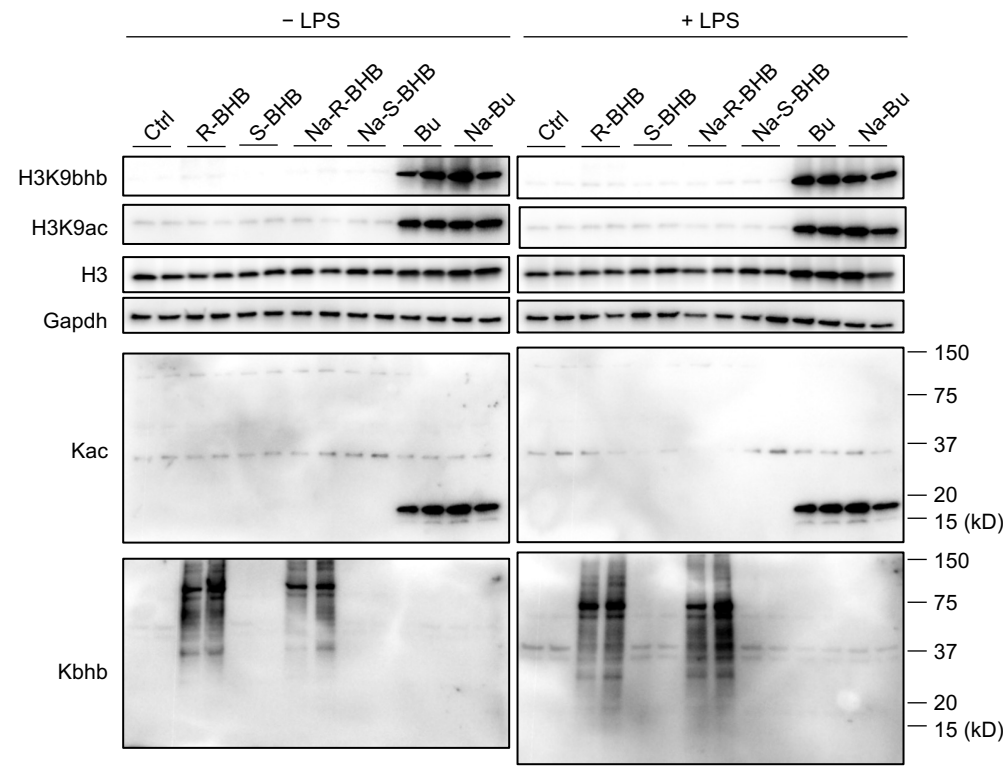


Supplemental Figure 20, related to Figure 3

(A) Mouse primary astrocytes (qPCR)



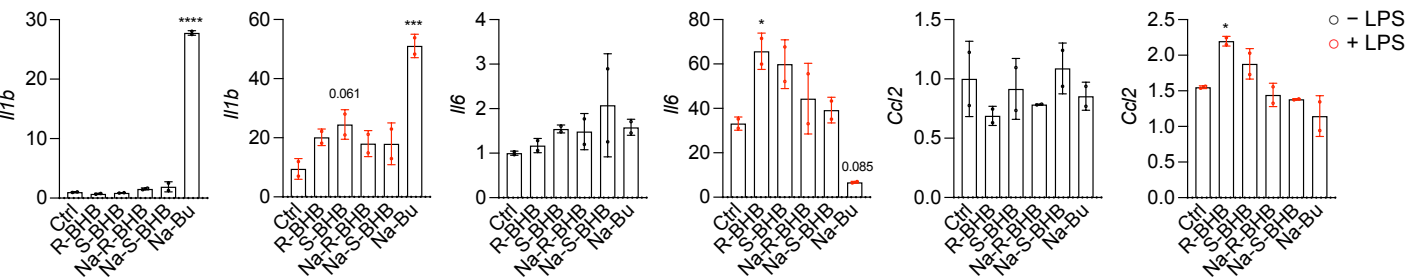
(B) Mouse primary astrocytes (WB)



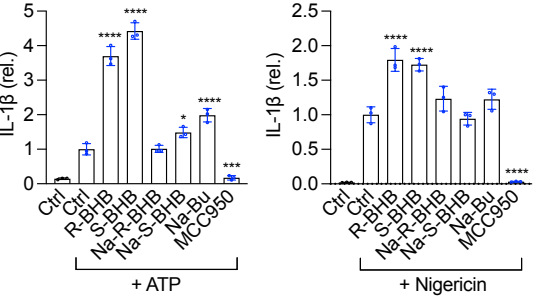


Supplemental Figure 21, related to Figure 3

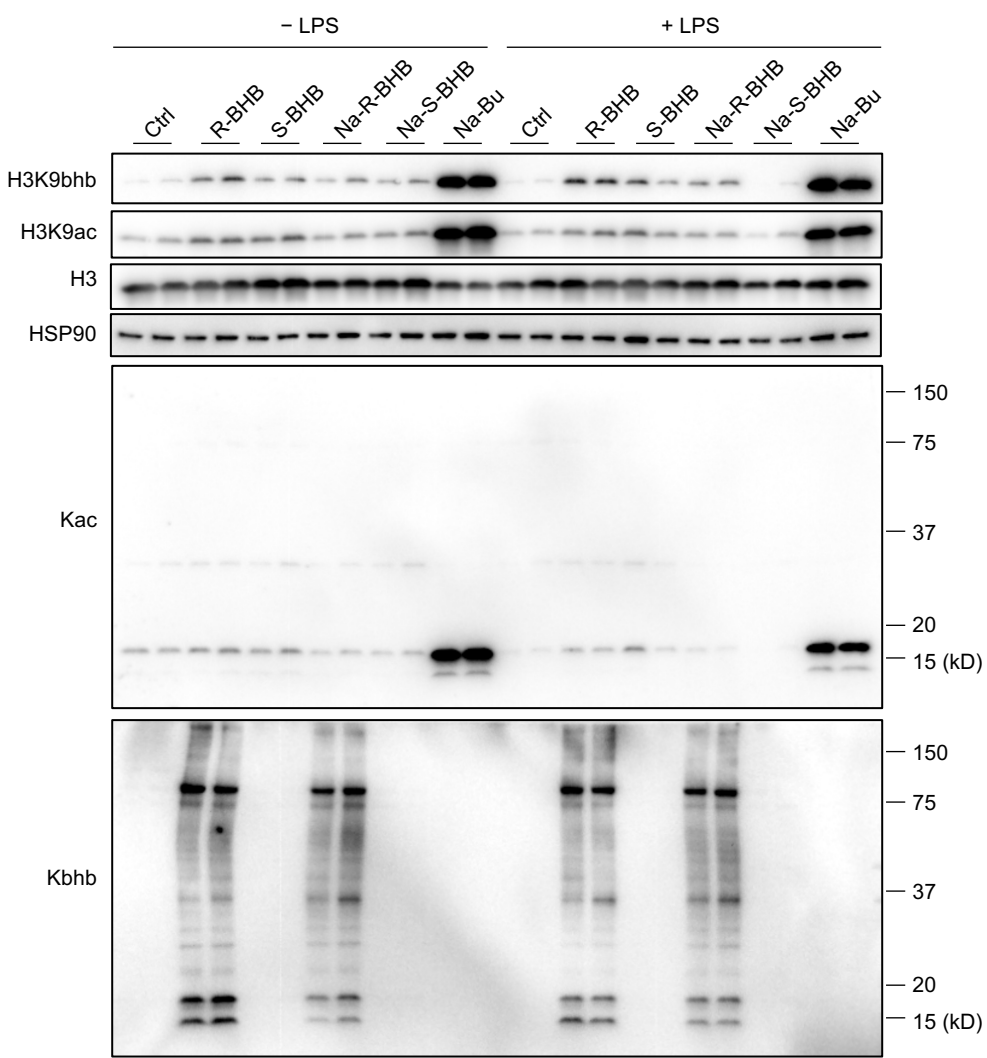
(A) Mouse IMG microglial cells (qPCR)



(B) Mouse IMG cells (ELISA)

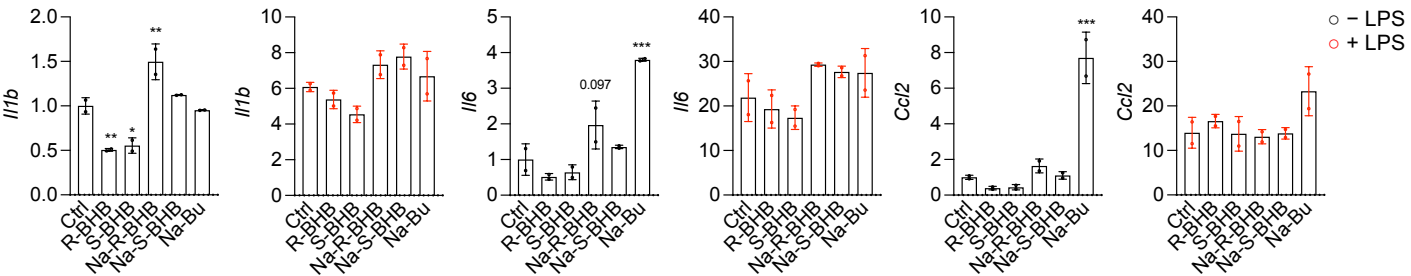


(C) Mouse IMG cells (WB)

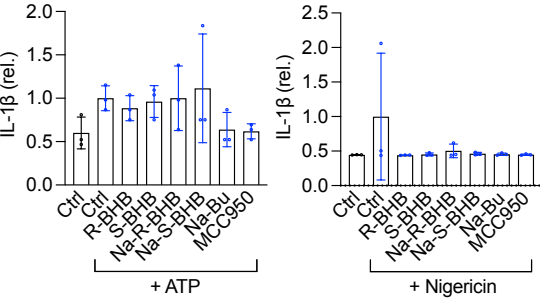


Supplemental Figure 22, related to Figure 3

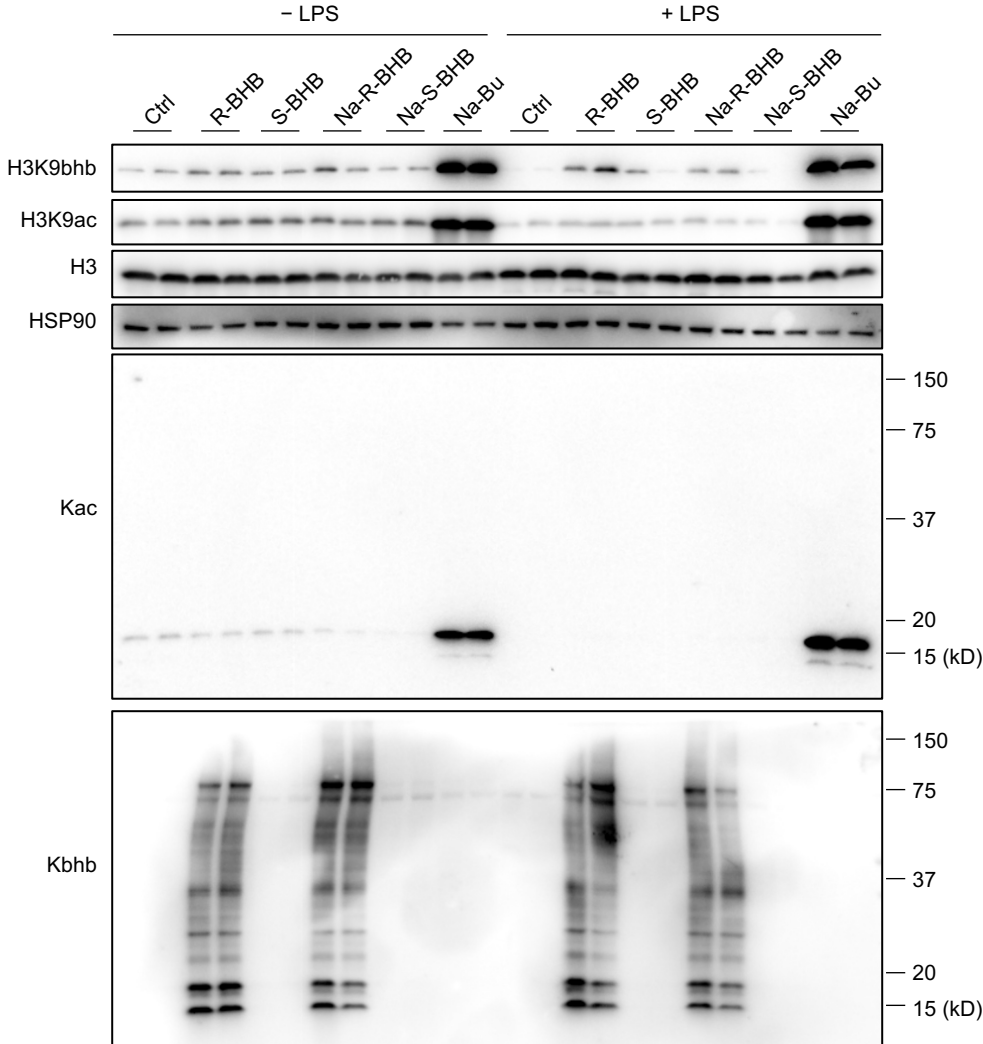
(A) Mouse BV-2 microglial cells (qPCR)



(B) Mouse BV-2 cells (ELISA)

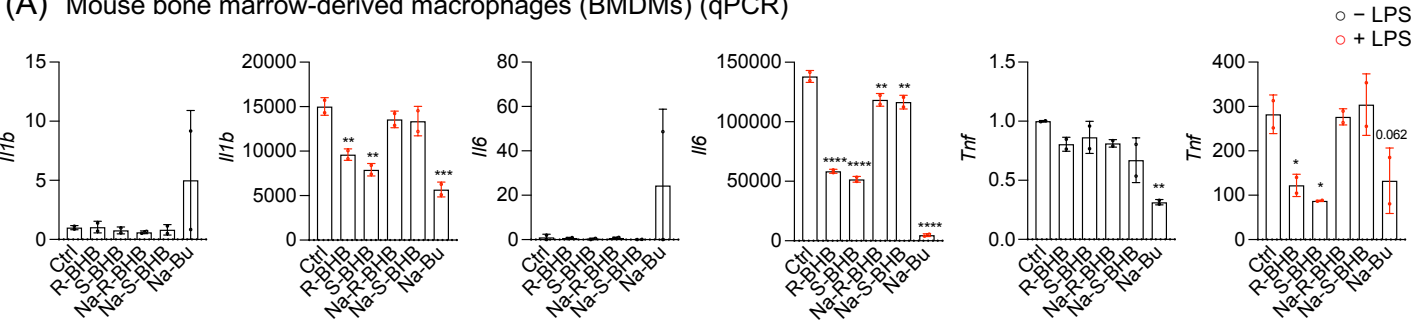


(C) Mouse BV-2 cells (WB)

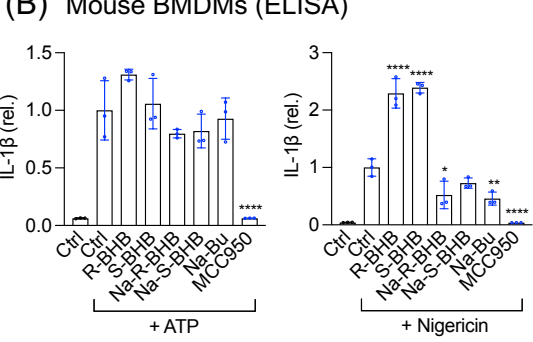


Supplemental Figure 23, related to Figure 3

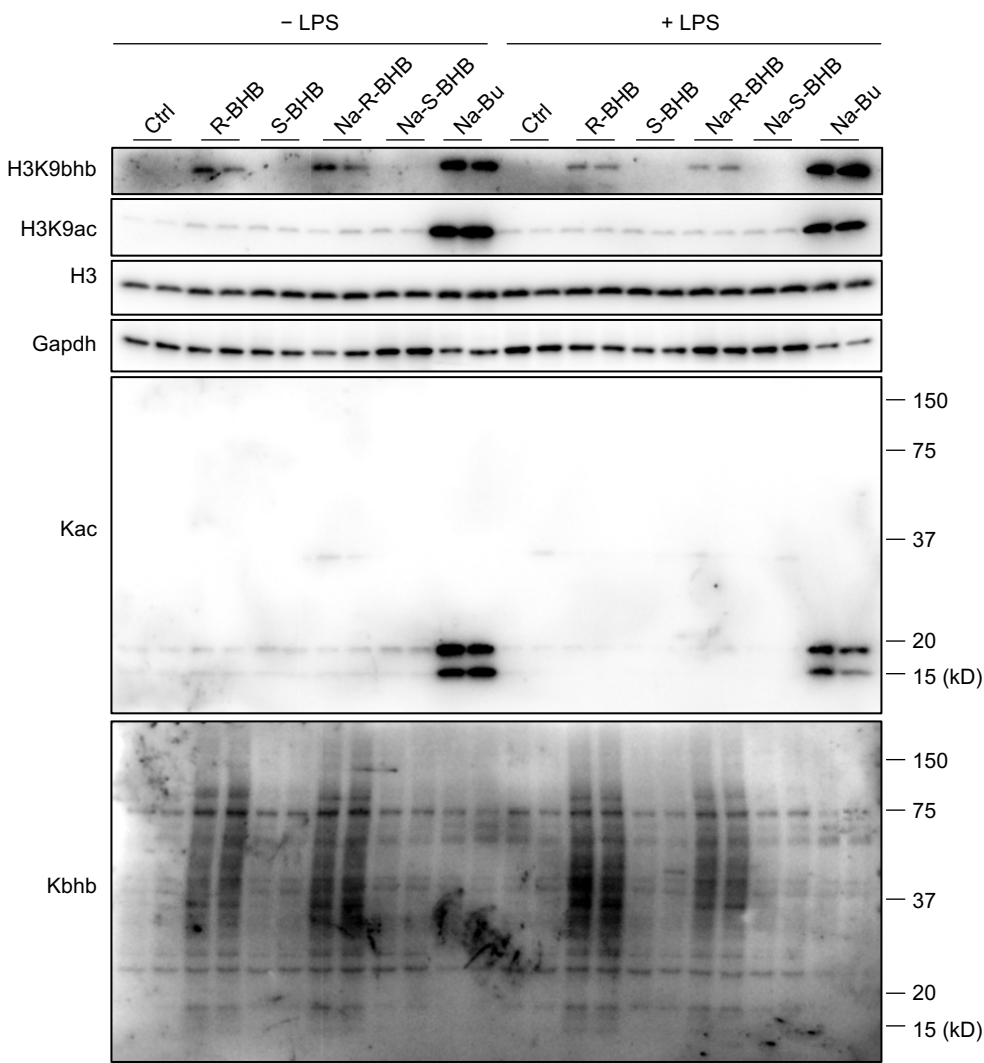
(A) Mouse bone marrow-derived macrophages (BMDMs) (qPCR)



(B) Mouse BMDMs (ELISA)

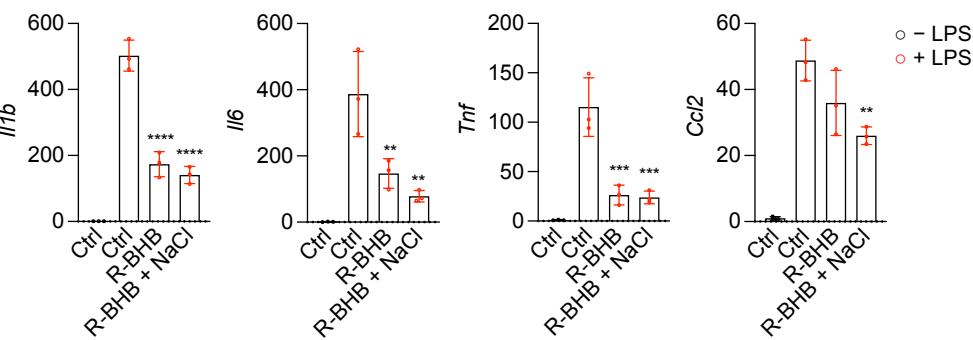


(C) Mouse BMDMs (WB)



Supplemental Figure 24, related to Figure 4

(A) Mouse primary microglia ± R-BHB (10 mM) ± NaCl (10 mM) (qPCR)



(B) Mouse primary microglia ± R-BHB (10 mM) ± NaOH (3.75 mM) (ELISA)

