

SUPPLEMENTARY FIGURE LEGENDS

Supplementary Figure 1. MCJ levels in livers of younger *Mat1a*-KO mice and MAT1A and DNAJC15 expression in human hepatic cells. (A) MAT α 1 and MCJ protein levels by western blotting and densitometric quantification in liver lysates from 2.5-month-old WT and *Mat1a*-KO mice. (B) *Dnajc15* mRNA levels in livers from 2.5-month-old WT and *Mat1a*-KO mice. (C) Cell identification of human liver cells. t-distributed stochastic neighbor embedding (t-SNE) of single-cell RNA-sequencing (scRNA-seq) 24,548 cells (12,274 cells/group) was generated by Seurat and colored by metadata of disease ontology label in single cell portal. (D) Gene expression of *MAT1A* and *DNAJC15* in t-SNE plot and Ridge plot.

Supplementary Figure 2. MAT α 1 levels in livers of *Mcj*-KO mice, and MCJ levels in livers of *Phb1*-KO mice. (A) MAT α 1 levels by western blotting in total and mitochondrial fractions of WT and *Mcj*-KO mouse livers. (B) MCJ levels by western blotting and in liver lysates from WT and liver-specific *Phb1*-KO mice. (C) *Phb1* and (D) *Dnajc15* mRNA levels by RT-PCT in livers from WT and *Phb1*-KO mice. *P<0.01 *Phb1*-KO vs WT.

Supplementary Figure 3. SAME lowers MCJ expression in a time- and dose-dependent manner in liver cell lines. MCJ levels by western blotting and quantification (lower panels) in HepG2, Huh-7 and SAME-D cells treated with (A) SAME 500 μ M for the indicated time points and (B) SAME at the indicated doses for 24 hours. (C) Viability of HepG2, Huh-7 and SAME-D cells after SAME 500 μ M treatment for the indicated time points. *P<0.01 SAME vs control.

Supplementary Figure 4. SAME reduces MCJ protein levels in other cell types. MCJ protein levels by western blotting and densitometric quantification in RAW, RKO, HT-29, MCF-7, and LX-2 cells treated with SAME 500 μ M for 24 hours. *P<0.01 SAME vs control.

Supplementary Figure 5. Effect of SAME on OXPHOS subunits and MCJ translation.

(A) Western blot analysis using an OXPHOS antibody cocktail which detects ATP5A (Complex V), UQCRC2 (Complex III), SDHB (Complex II), and NDUFB8 (complex I) in lysates of livers of WT mice, Huh-7, and HepG2 cells treated with SAME. Densitometric quantification is shown below. (B) *DNAJC15* mRNA translation in polysomes in Huh-7 cells treated with SAME for 24 hours.

Supplementary Figure 6. MCJ methylation. (A) MCJ lysine and arginine methylation predictions. (B) Spectra of methylated MCJ at Lys83. Representative spectra obtained from DDA-MS acquisitions in MCJ immunoprecipitations showing all of the ions used to identify the peptide containing MCJ Lys83. (C) MCJ-HA levels by western blotting and quantification in Huh-7 cells after MCJ WT, K72A, K83A, K89A, K107A and K125A overexpression for 48 hours and 24 hours of SAME treatment.

Supplementary Figure 7. MCJ is upregulated in ALD. (A) MCJ levels by immunohistochemistry in all the normal and AH human liver samples at 20x and 40x magnification. (B) *Dnajc15* levels by RT-PCR in livers from pair-fed and ethanol-fed mice following the NIAAA model and (C) AML-12 cells treated with ethanol 100mM for 48 hours. (D) MCJ and MAT α 1 levels by western blotting in AML-12 cells treated with ethanol 100mM for 24 and 48 hours.

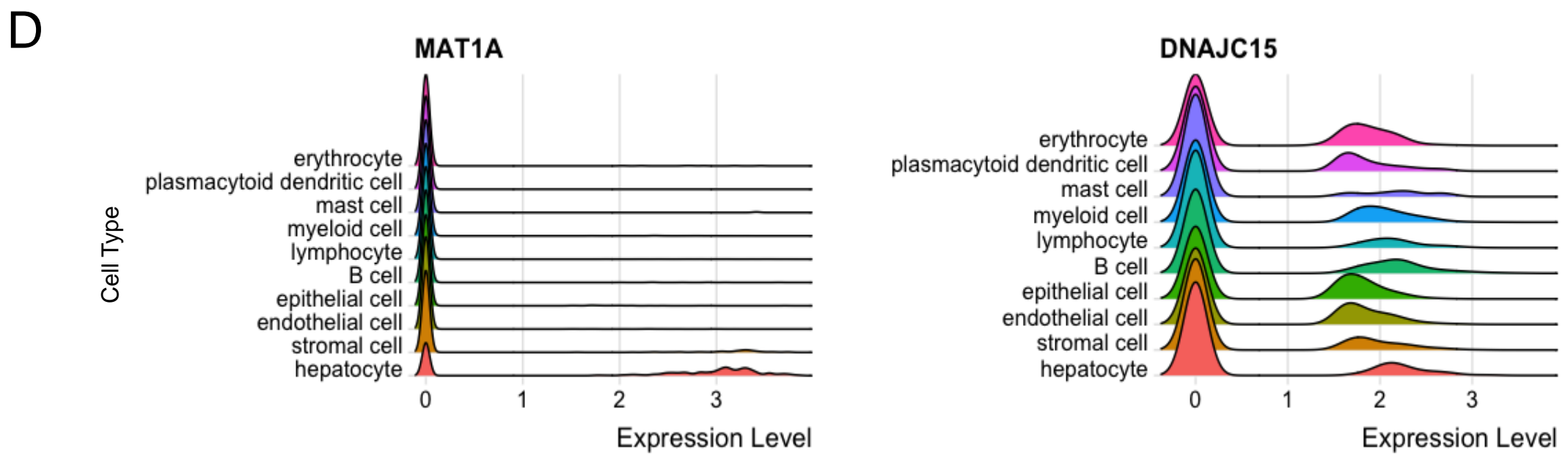
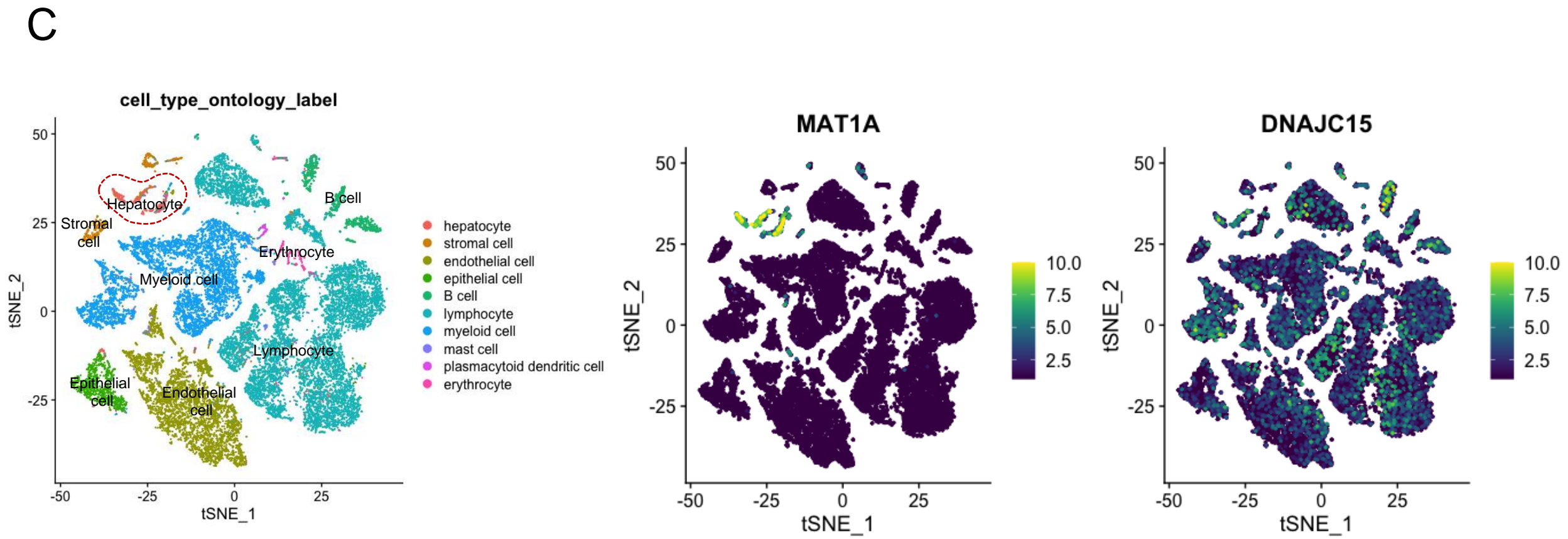
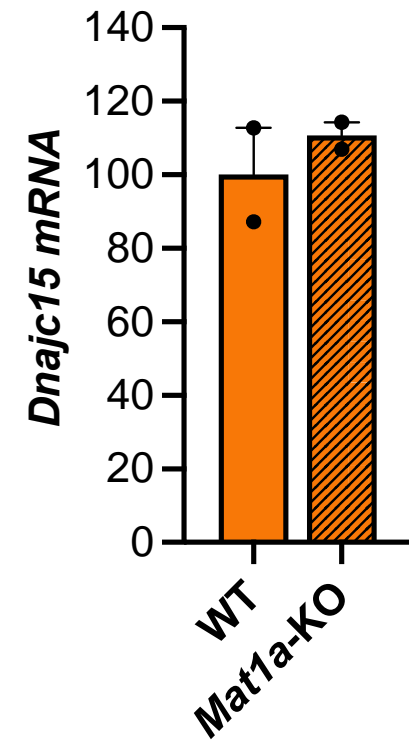
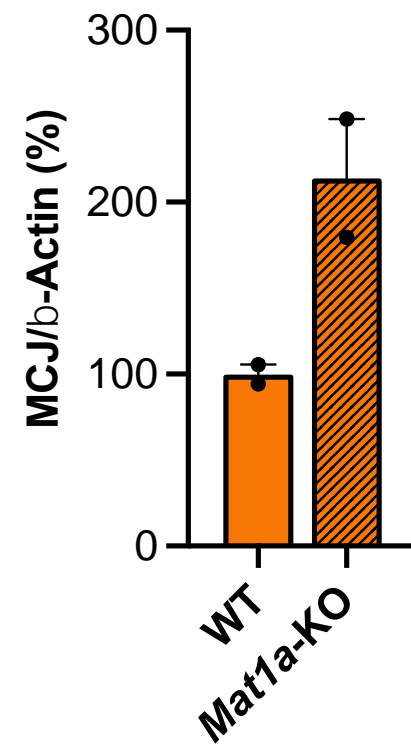
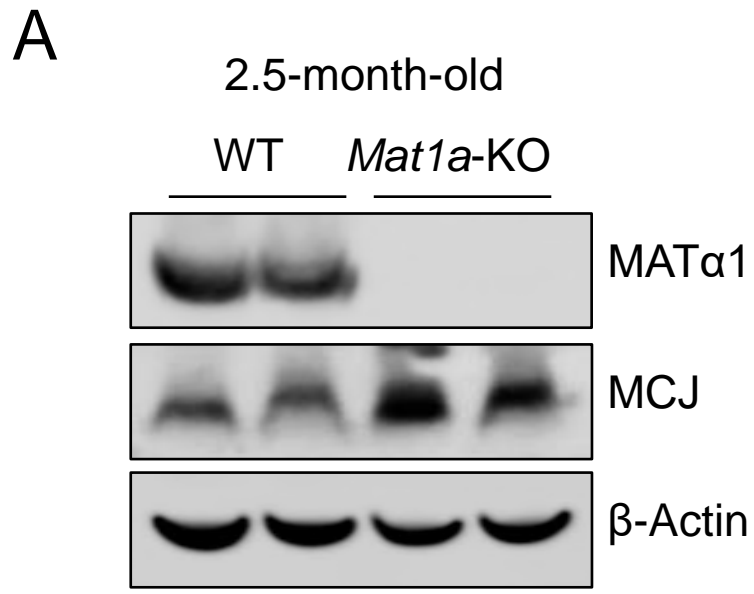


Figure S1

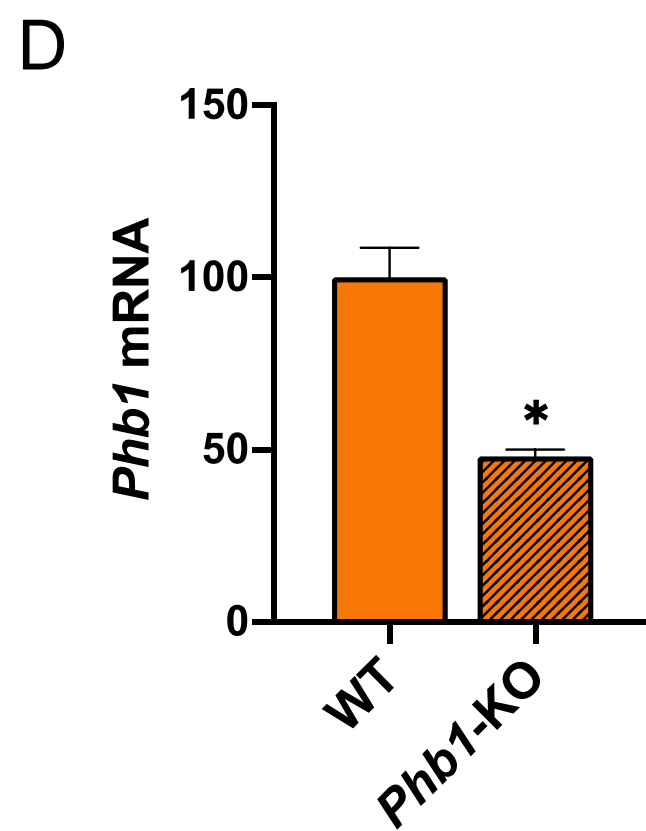
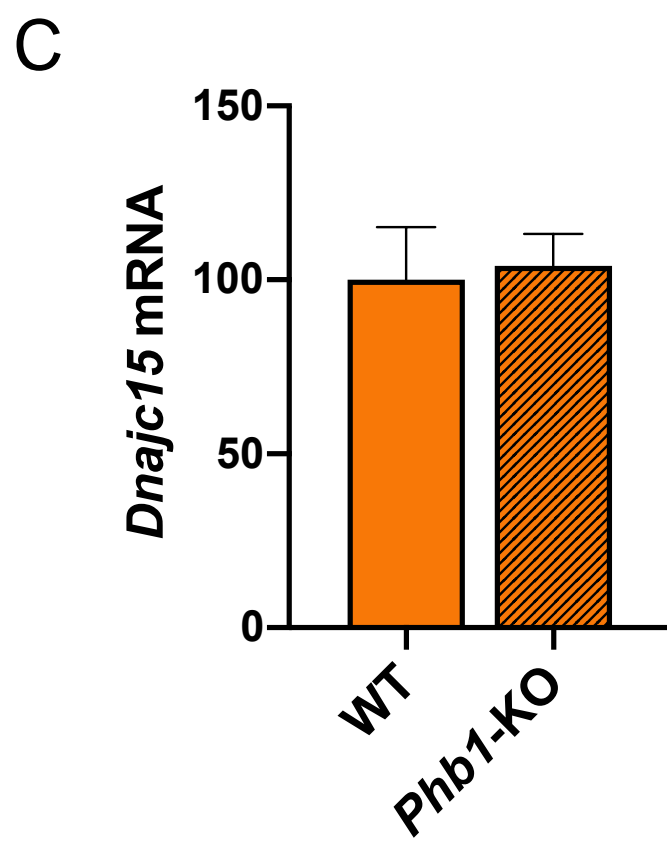
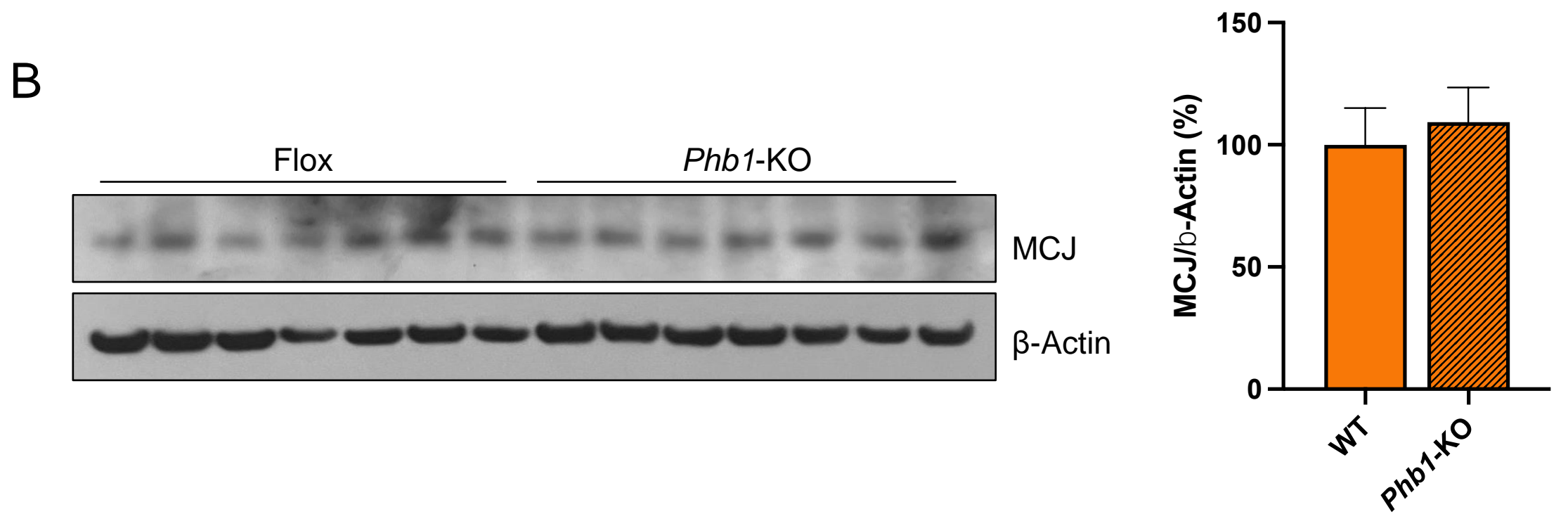
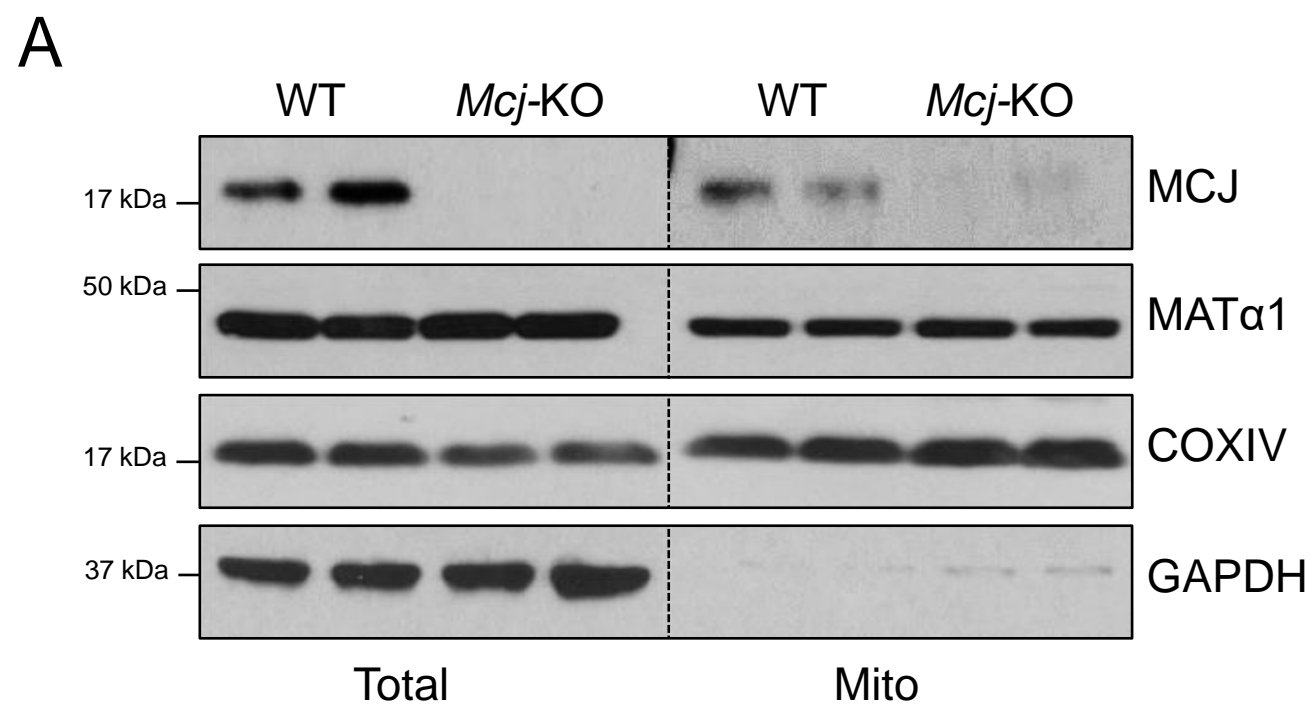


Figure S2

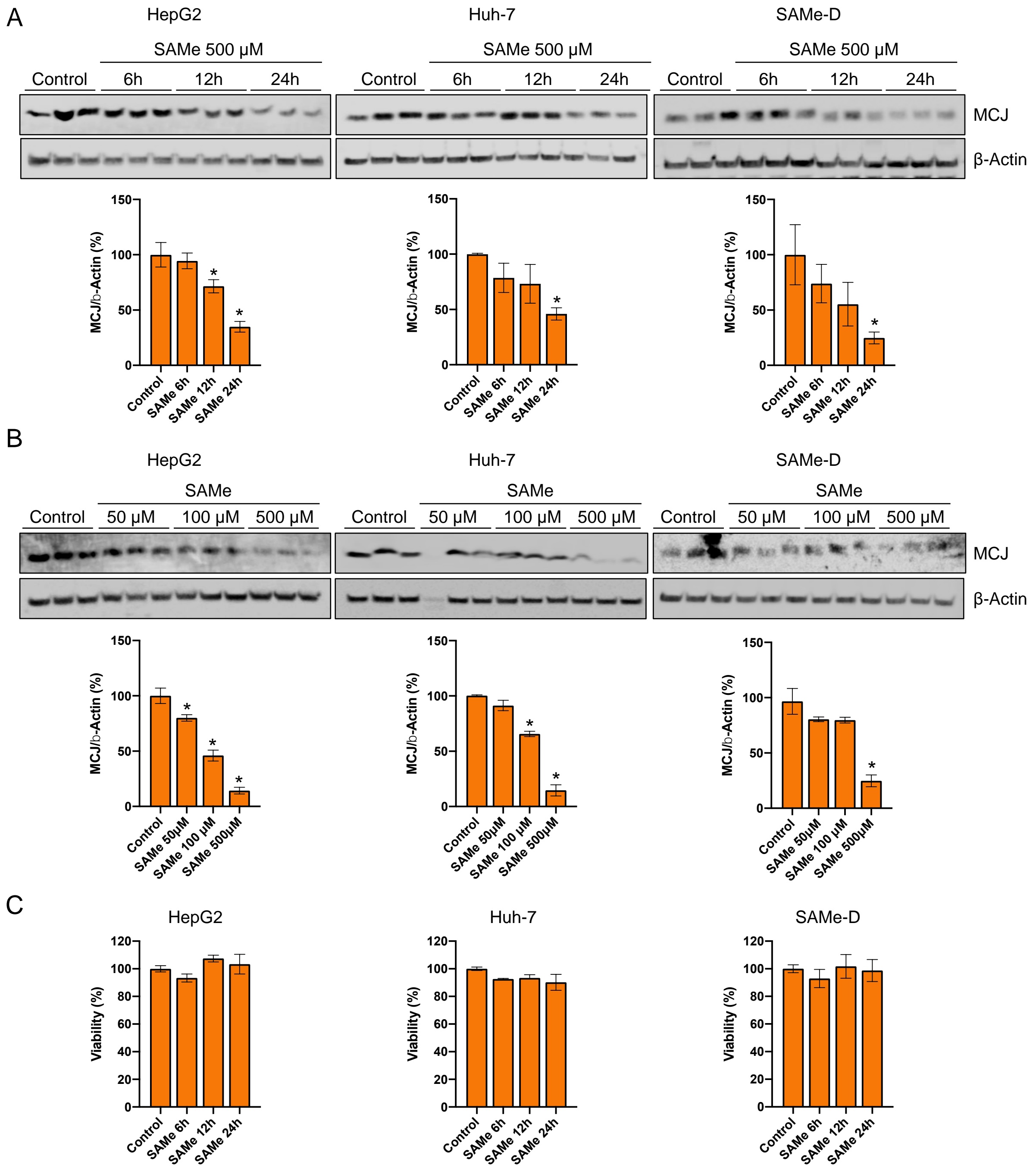


Figure S3

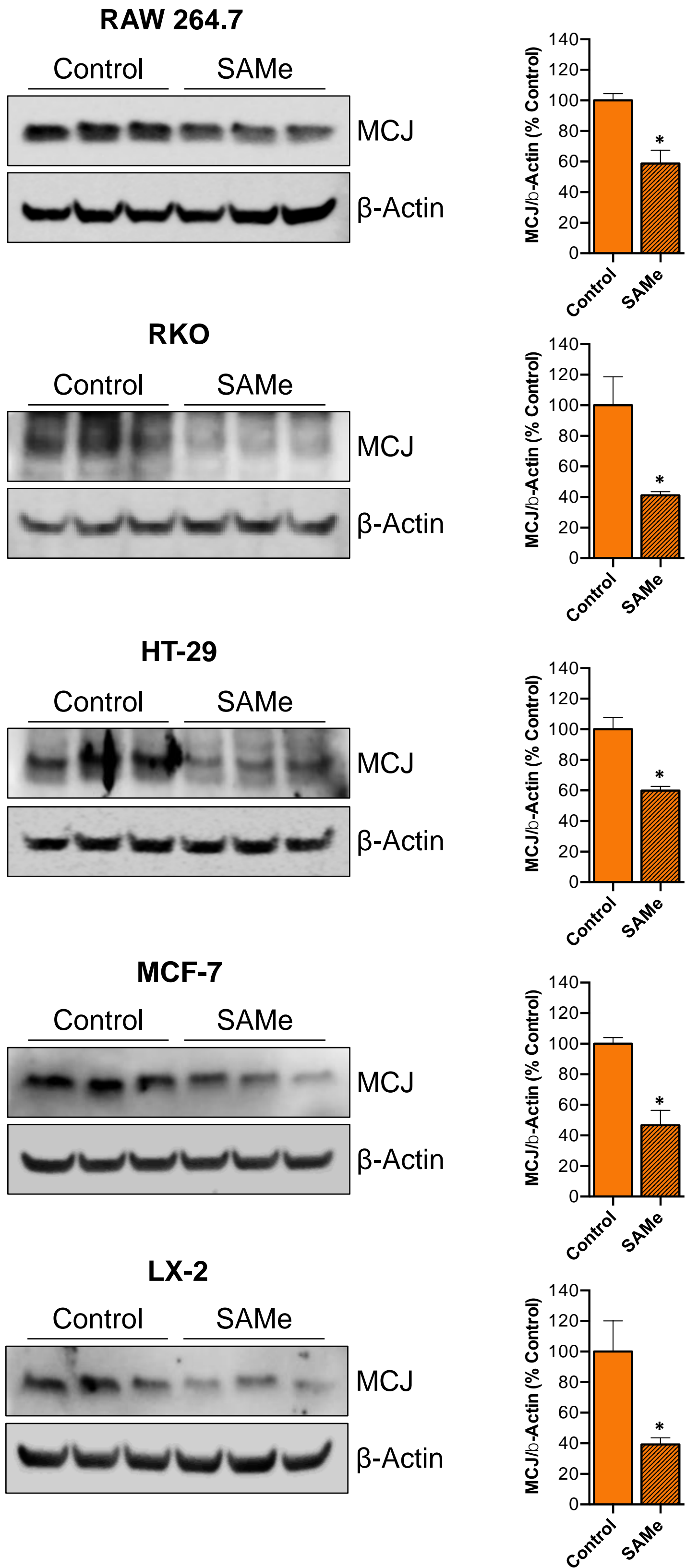
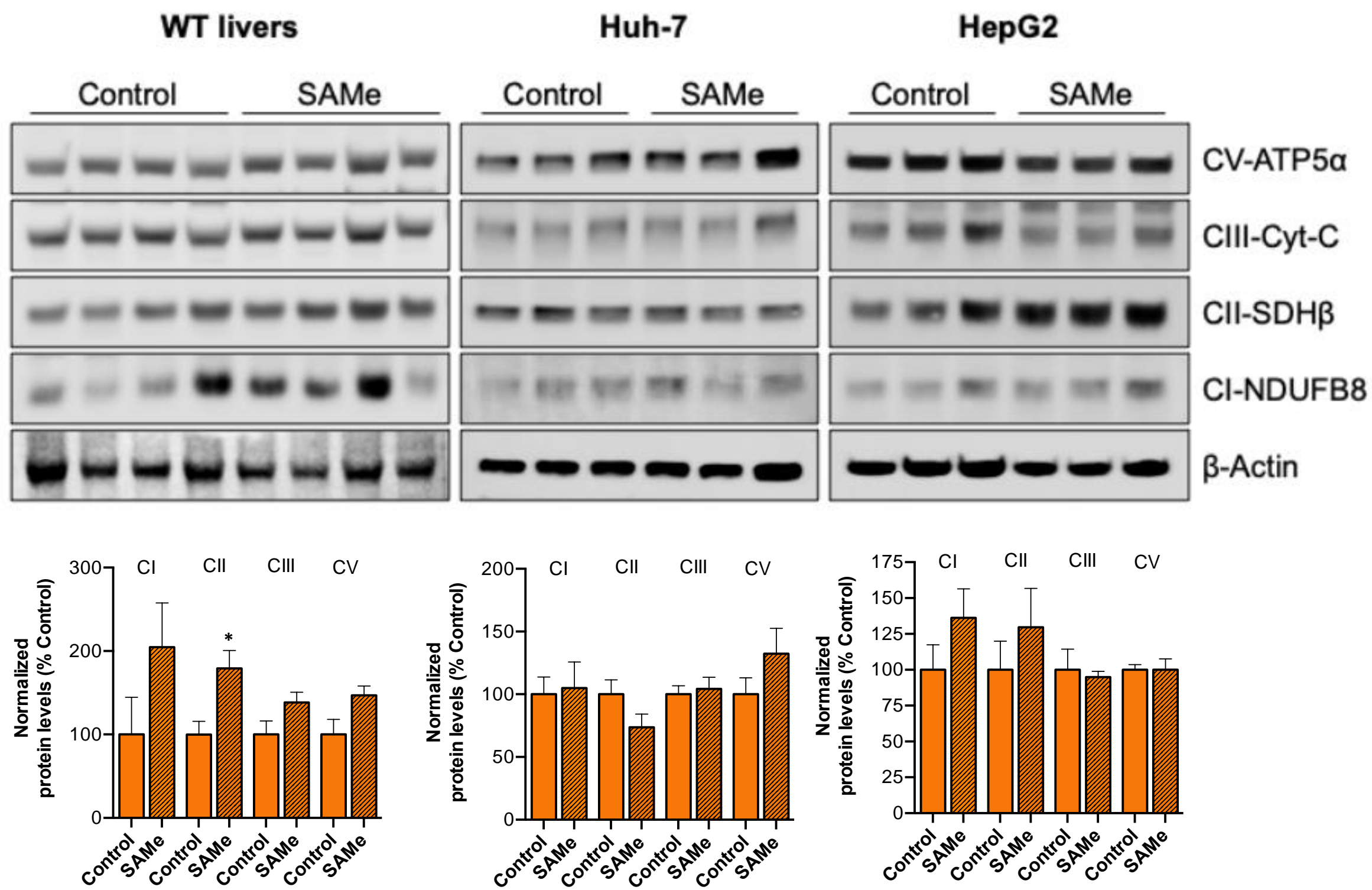


Figure S4

A



B

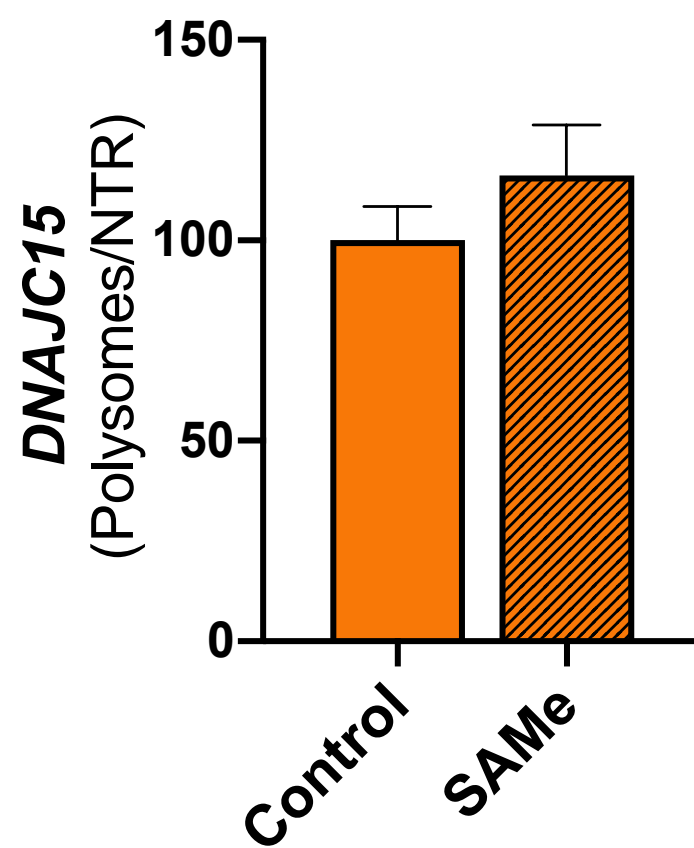


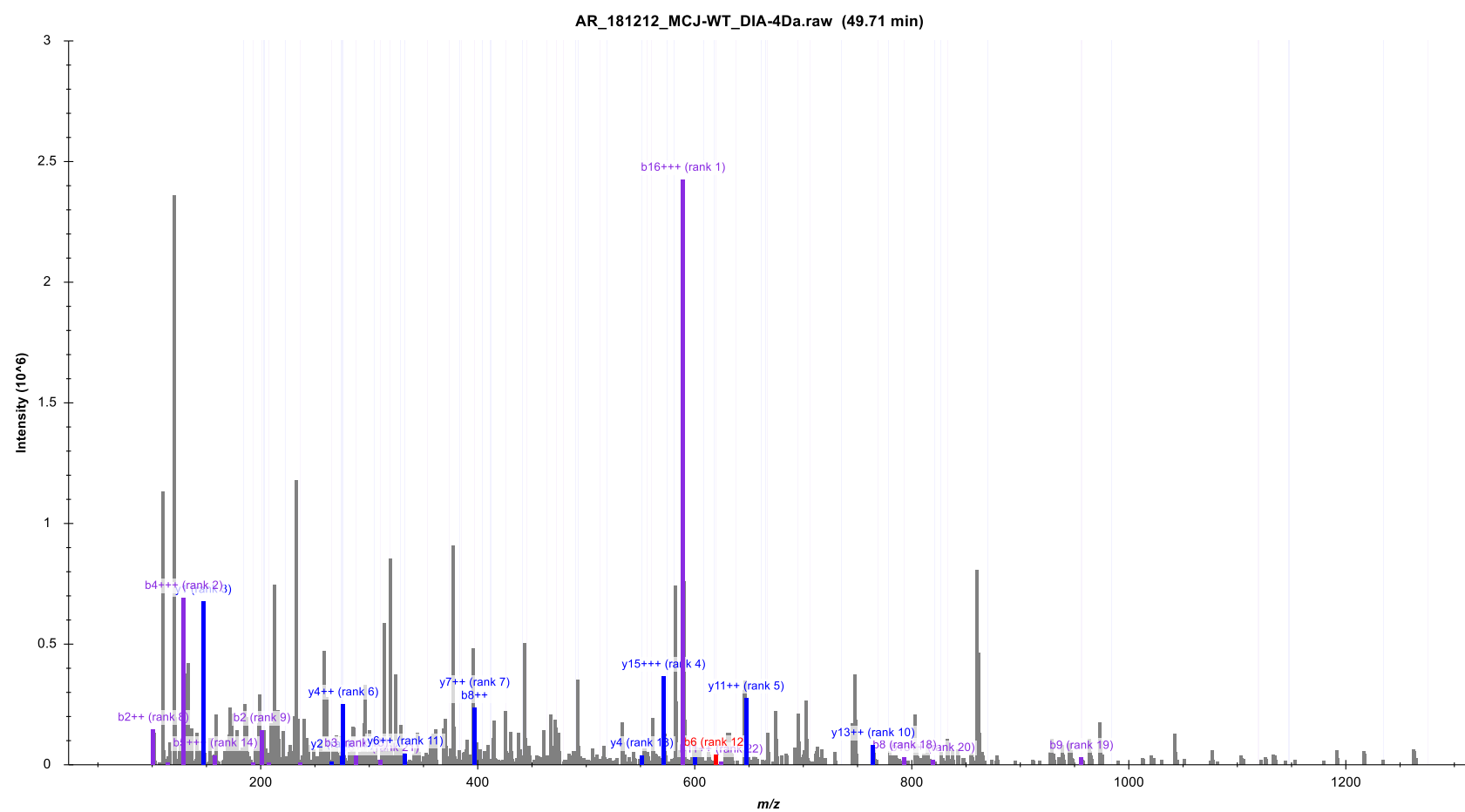
Figure S5

A

Lysine-methylation (Hs/Mm)			Arginine-methylation (Hs/Mm)		
GPS-MSP	Malab	PSSME	GPS-MSP	Malab	PSSME
25/23	25/23	-	4/2	-	4/2
74/72	74/72	74/72	35/33	-	35/33
85/83	85/83	85/83	55/53	-	55/53
91/89	91/89	91/89	94/92	-	94/92
109/107	109/107	109/107			
111/109	-	111/109			
127/125	127/125	127/125			
149/147	-	149/147			

B

Representative Spectra for ISSPSFSSYYKGGFEQK



C

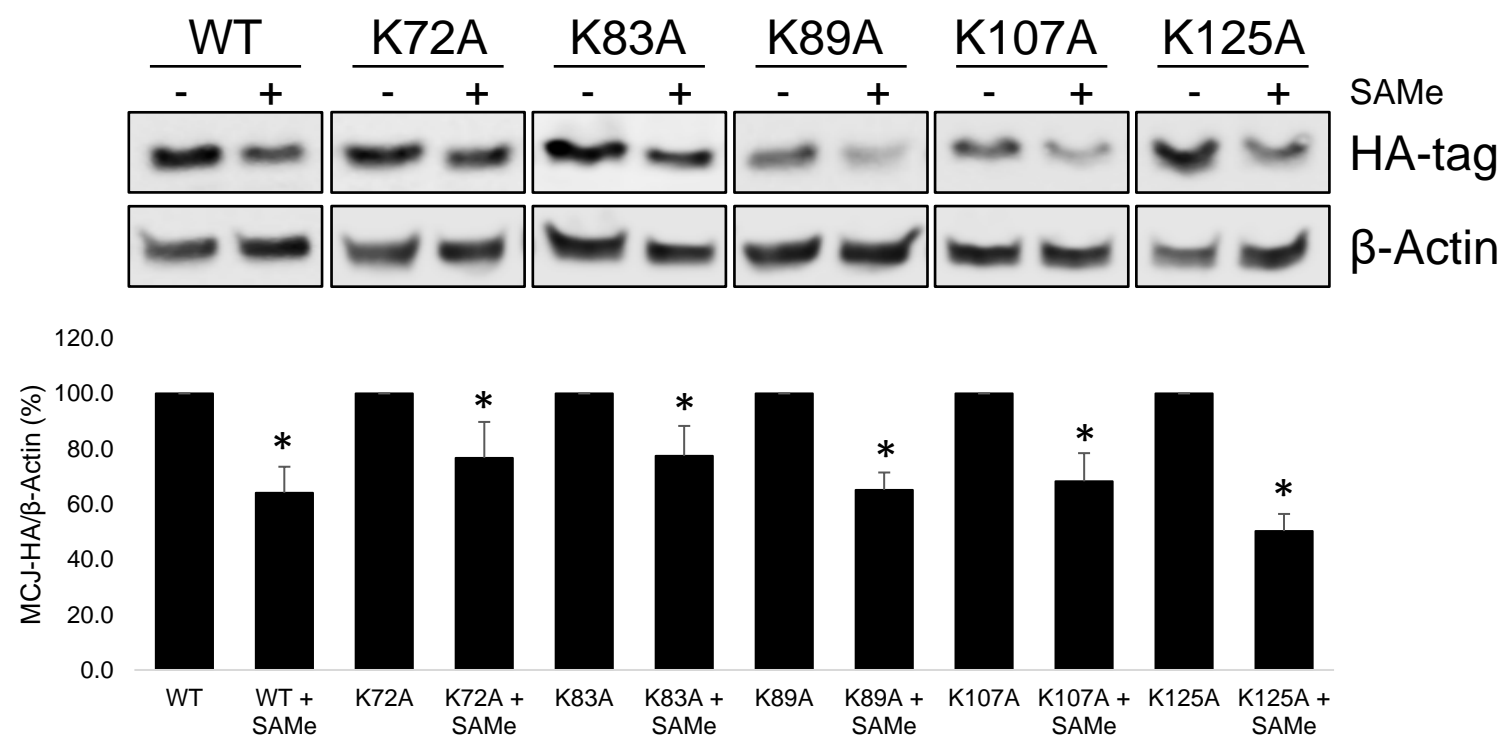
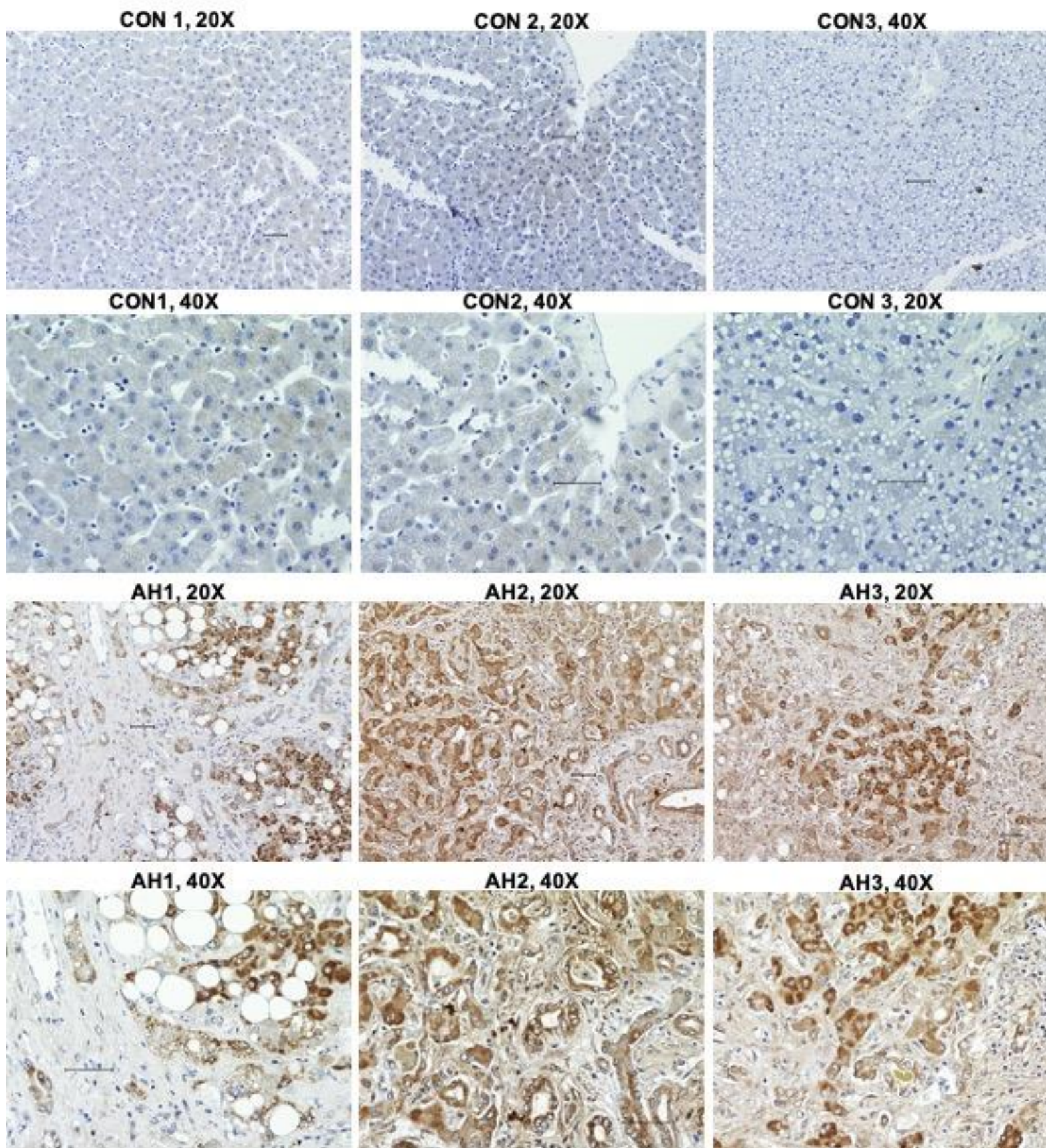
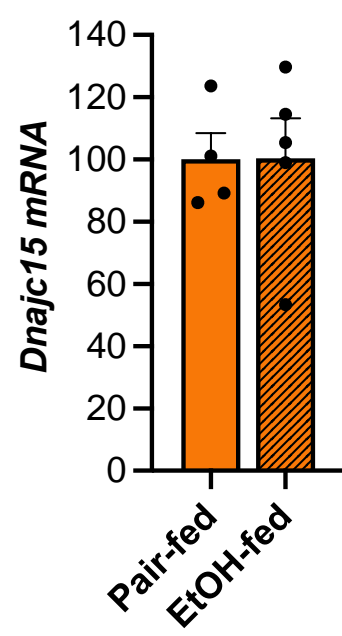


Figure S6

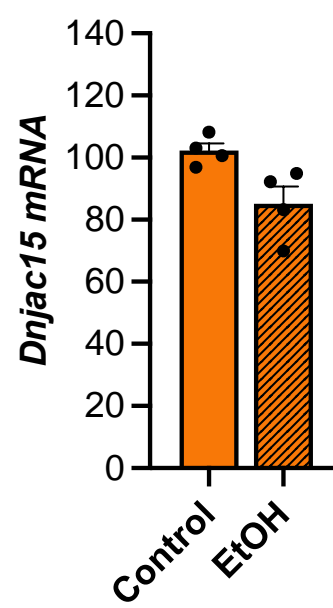
A



B



C



D

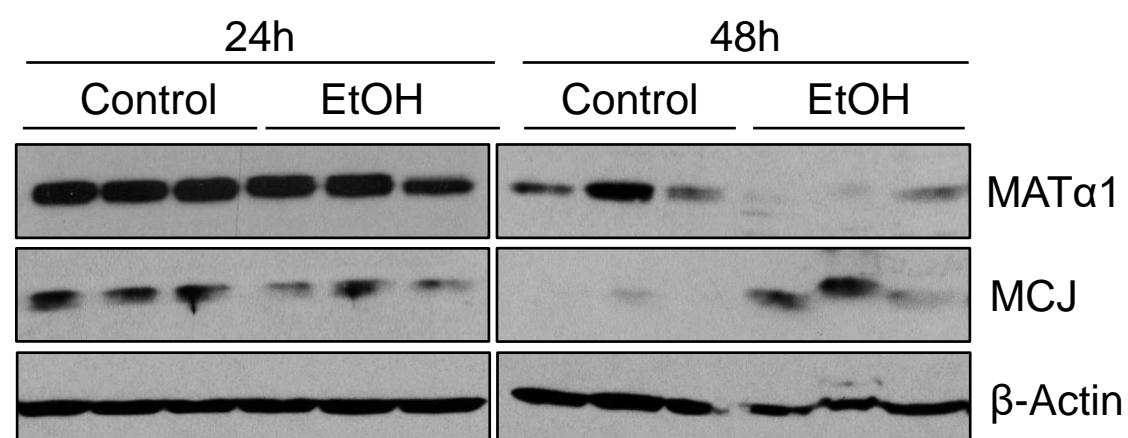
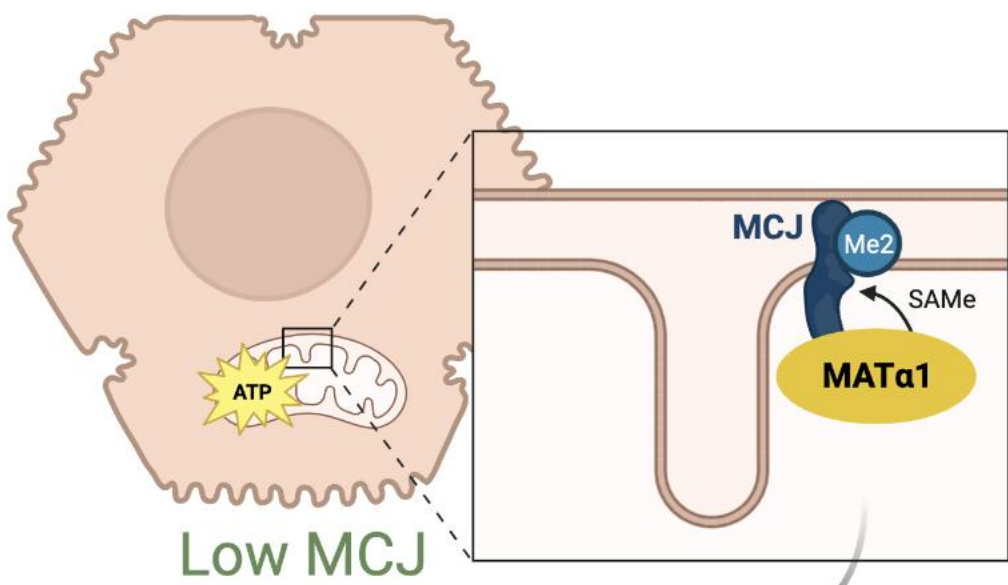


Figure S7

HEALTHY LIVER



High MAT1A
High SAMe

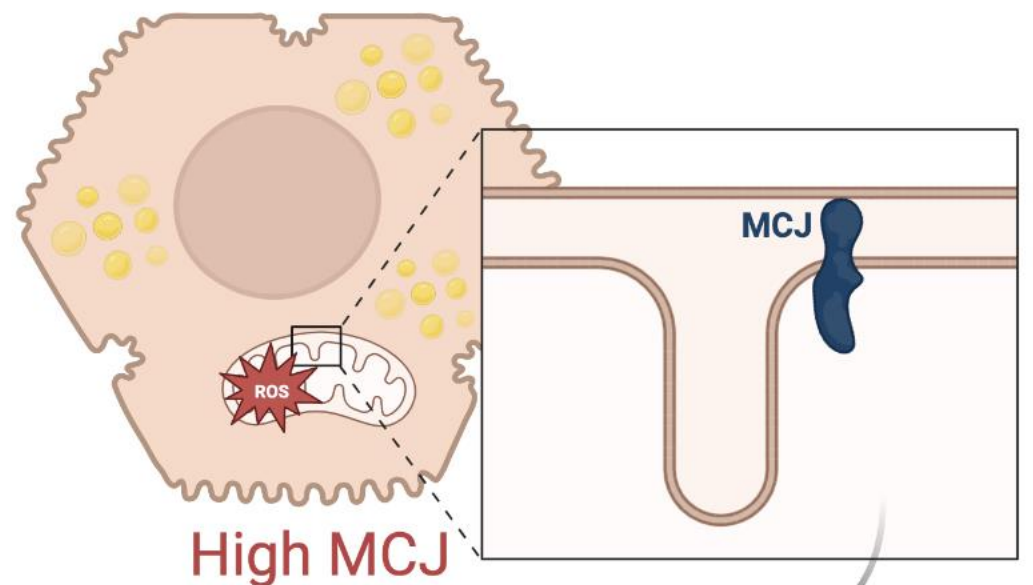


MCJ degradation

ALCOHOL



Low MAT1A
Low SAMe



MCJ degradation