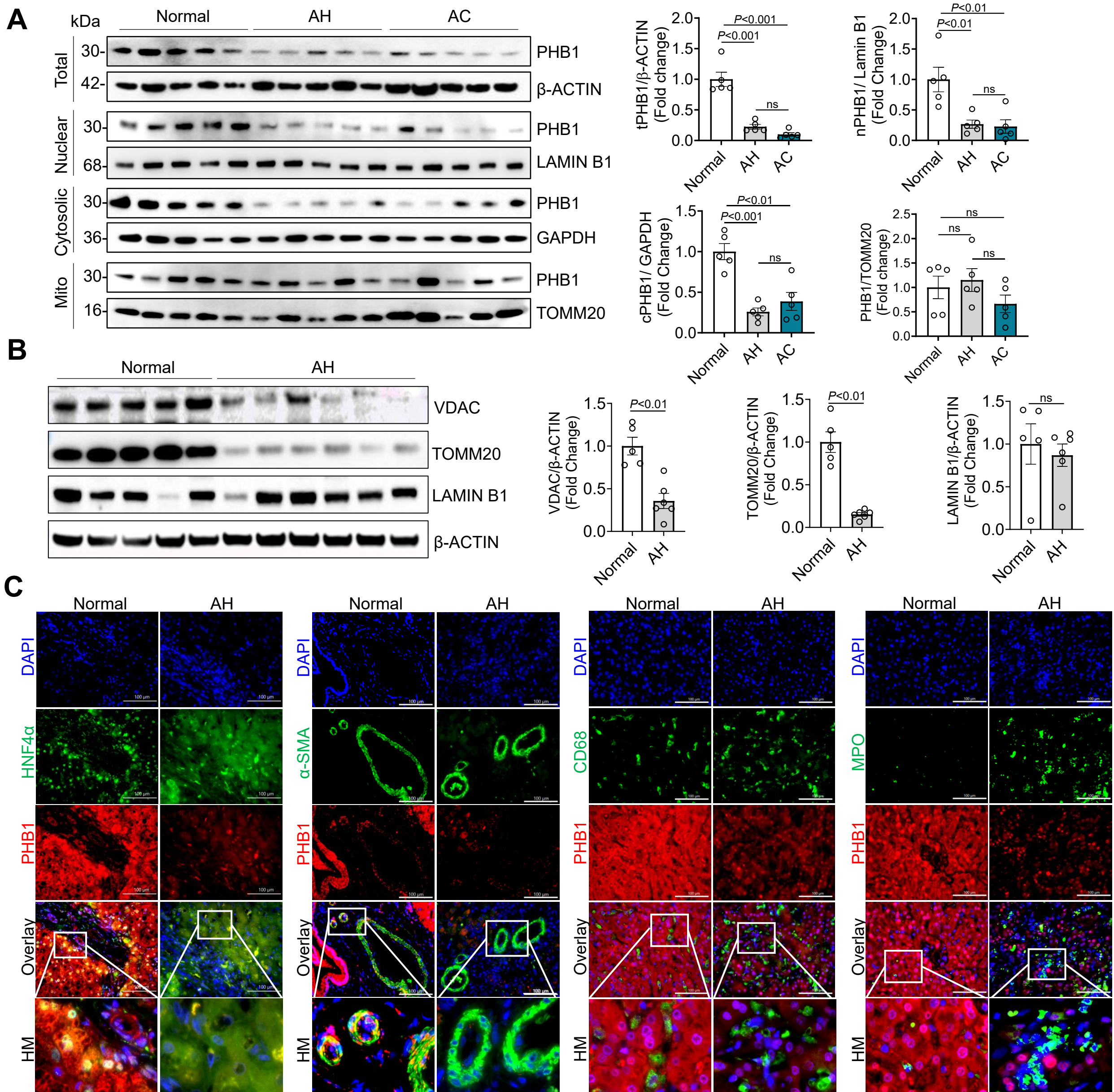
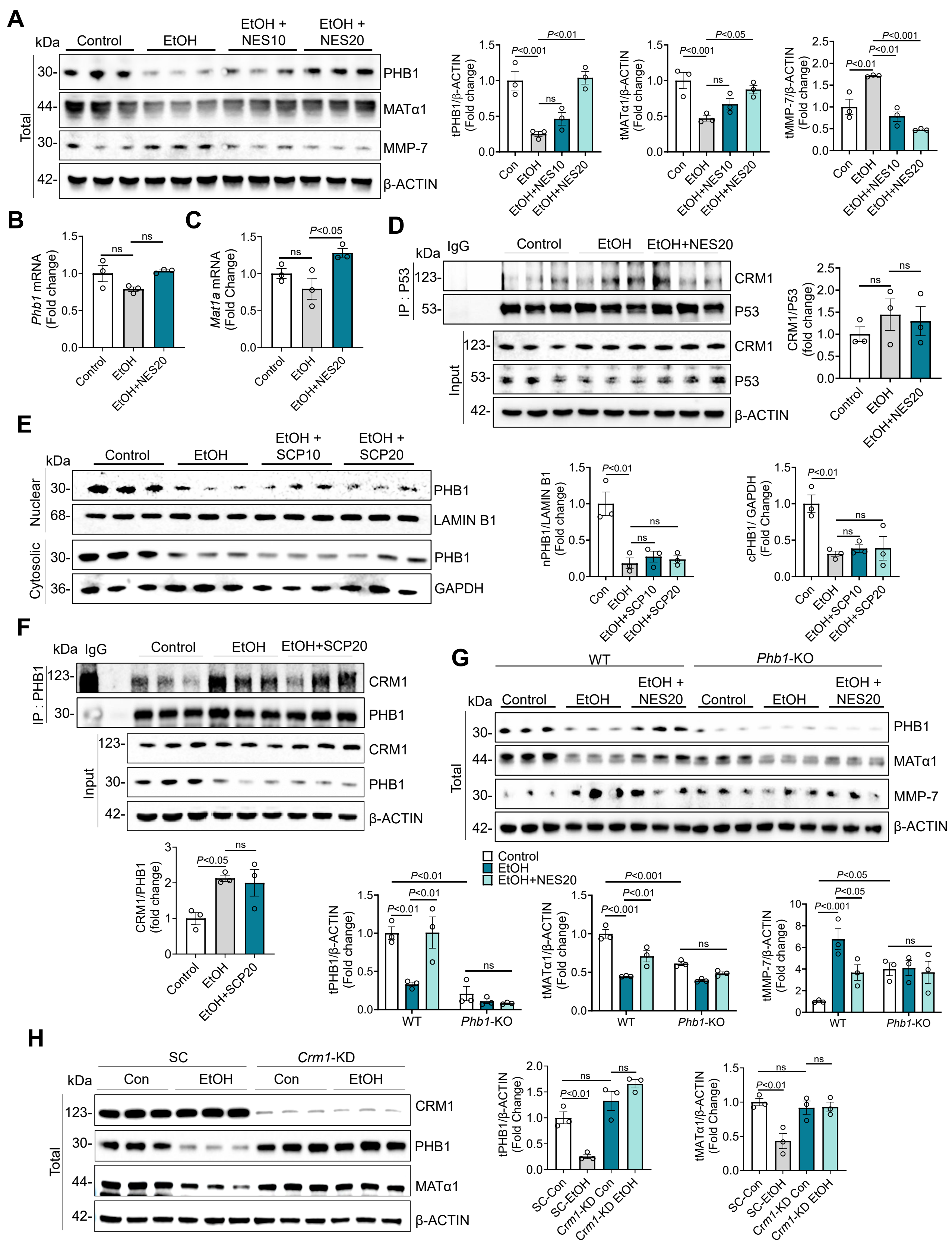




Supplemental Figure S1:

- (A) Immunoblot images of total, nuclear, cytosolic, and mitochondrial PHB1 in normal human liver, alcoholic hepatitis (AH) and alcoholic cirrhosis (AC) samples (n=5). Densitometric quantification is shown to the right of the blots.
- (B) Immunoblot images of total VDAC, TOMM20 and LAMIN B1 in normal human liver and alcoholic hepatitis (AH) samples (n≥5). β-ACTIN was used as loading control. Densitometric quantification is shown on the right of the blots.
- (C) Representative immunofluorescence images of liver sections from normal and AH patients, co-stained with PHB1 (red) and cell-type-specific markers (green: HNF4α/α-SMA/CD68/MPO), with nuclei counterstained with DAPI (blue) and merged overlay images, with boxed regions (HM, high magnification). Scale bars, 100 μm.

Statistical significance was assessed by one-way ANOVA with Tukey's post-hoc correction and two-tailed T-test (Panel B). Significance is denoted with $P<0.01$, and $P<0.001$ and ns represents not significant.

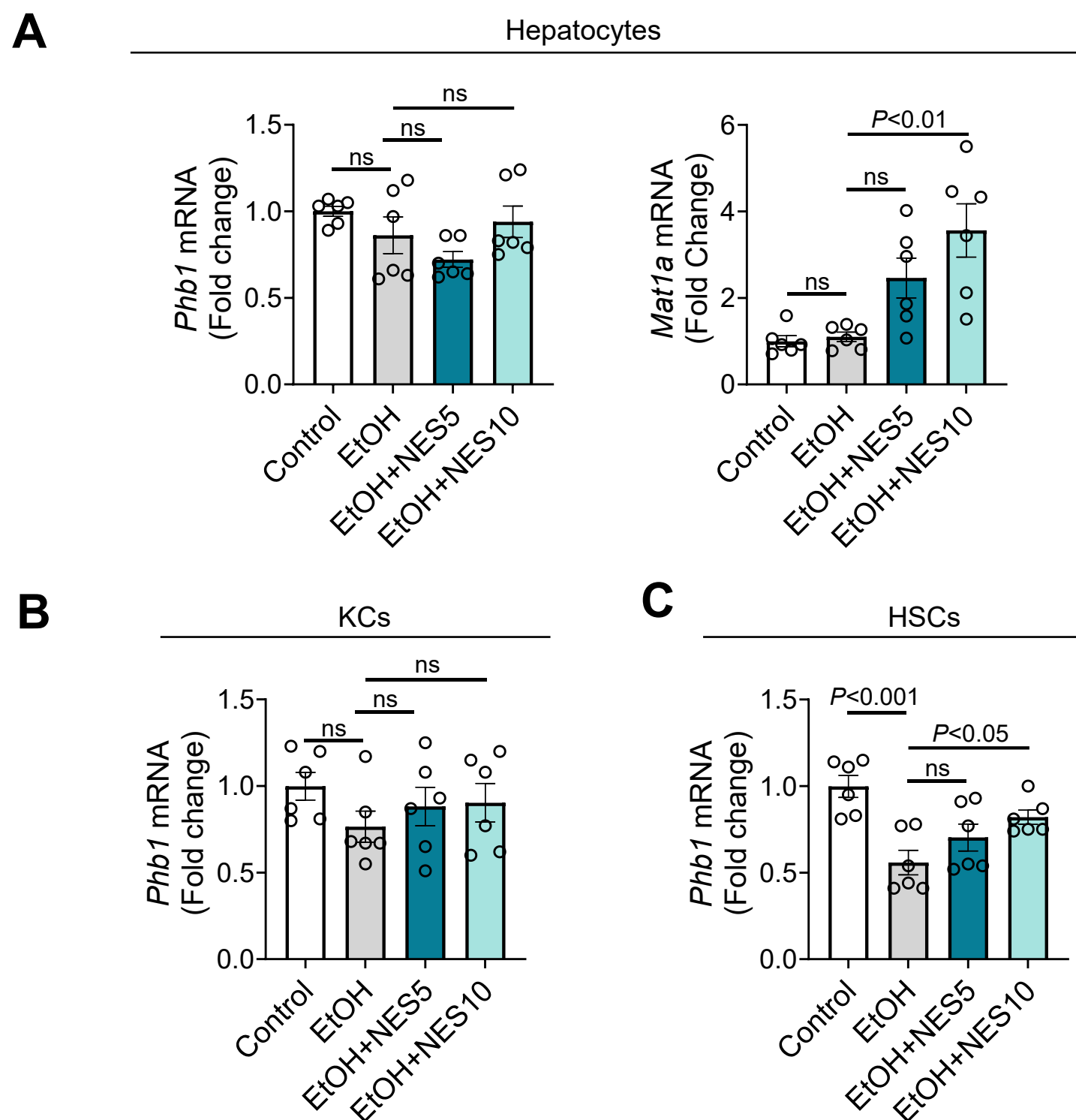


Supplemental Figure S2

Supplemental Figure S2:

- (A) Immunoblot images of Total PHB1, MAT α 1 and MMP-7; β -ACTIN was used as loading control. Quantification (right) shows fold changes relative to control (n=3).
- (B) mRNA expression of *Phb1* in primary mouse hepatocytes treated with EtOH $\pm$ NES (n=3).
- (C) mRNA expression of *Mata1* in primary mouse hepatocytes treated with EtOH $\pm$ NES (n=3).
- (D) Co-IP immunoblots demonstrating no change in interaction of P53 and CRM1 following treatment with NES in EtOH-treated hepatocytes (n=3). Densitometric quantification of CRM1/P53 is shown to the right of the blots.
- (E) Immunoblot images of nuclear and cytosolic PHB1 following treatment with scrambled peptide (SCP) in EtOH-treated hepatocytes; LAMIN B1 and GAPDH were used as loading controls, respectively. Quantification (right) shows fold changes relative to control (n=3).
- (F) Co-IP immunoblots demonstrating no change in interaction of PHB1 and CRM1 following treatment with scrambled peptide (SCP) in EtOH-treated hepatocytes (n=3). Densitometric quantification of CRM1/PHB1 is shown below.
- (G) Western blot analysis comparing total PHB1, MAT α 1 and MMP-7 levels in wild-type (WT) and *Phb1*-knockout (KO) hepatocytes following EtOH $\pm$ NES treatment (n=3). β -ACTIN was used as loading control. The dashed line denotes two separate gels but were transferred to one membrane prior to development. Quantification (below) shows fold changes relative to control (n=3).
- (H) Immunoblot images of Total PHB1, MAT α 1 and CRM1 in CRM1 knockdown (CRM1-KD) primary mouse hepatocytes; β -ACTIN was used as loading control. Quantification (right) shows fold changes relative to control (n=3).

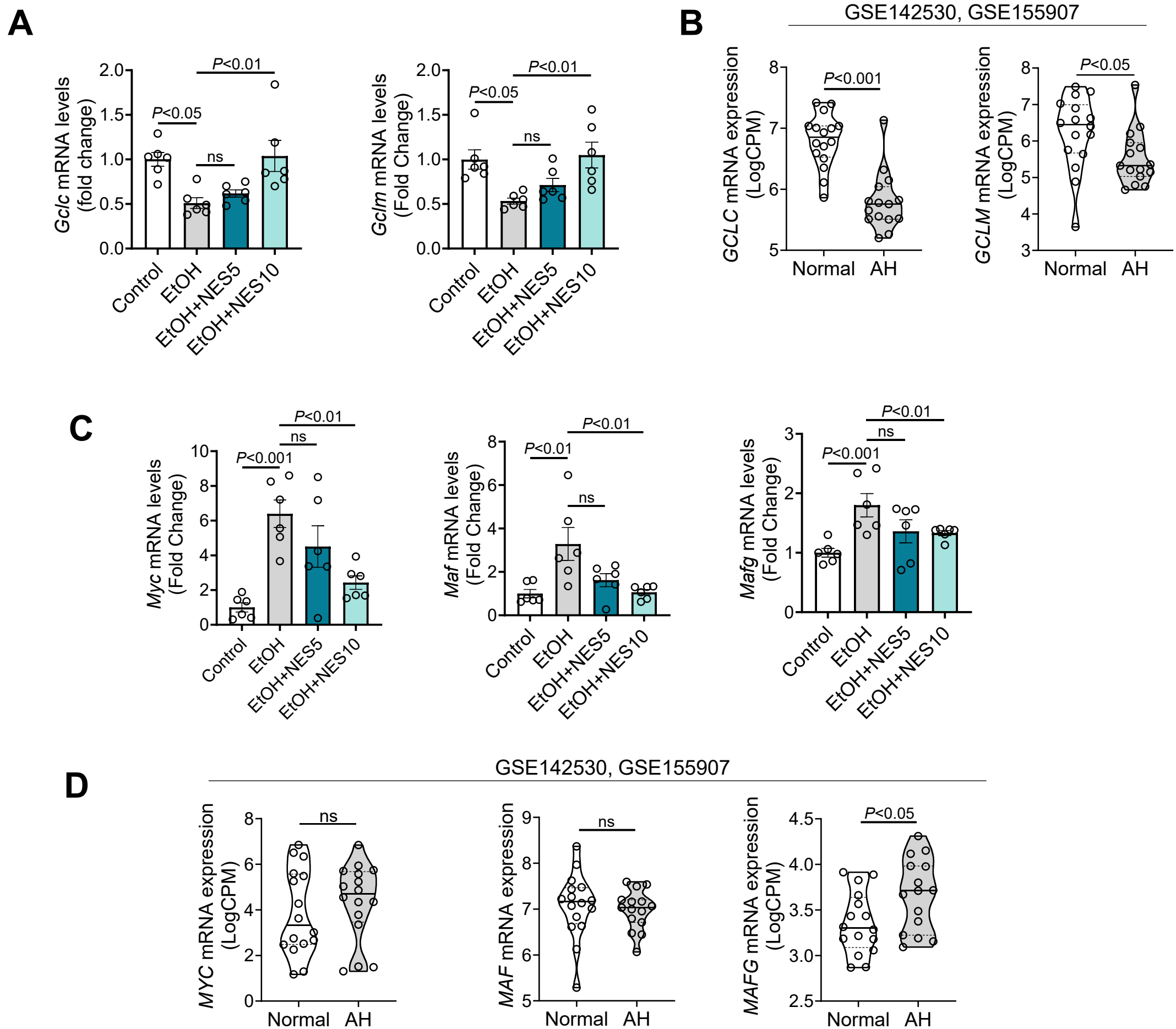
NES10 and NES20 represent 10 μ g/mL and 20 μ g/mL doses of NES. SCP20 represent 20 μ g/mL dose of SCP. Data are presented as mean $\pm$ SEM. Statistical significance was assessed by one-way ANOVA with Tukey's post-hoc correction. Significance is denoted with $P<0.05$, $P<0.01$, and $P<0.001$ and ns represents not significant.



Supplemental Figure S3:

- (A) mRNA expression of *Phb1* and *Mata1* in hepatocytes isolated from the liver of control and EtOH-fed mice with or without NES treatment (n=6).
- (B) mRNA expression of *Phb1* in KCs isolated from the liver of control and EtOH-fed mice with or without NES treatment (n=6).
- (C) mRNA expression of *Phb1* in HSCs isolated from the liver of control and EtOH-fed mice with or without NES treatment (n=6).

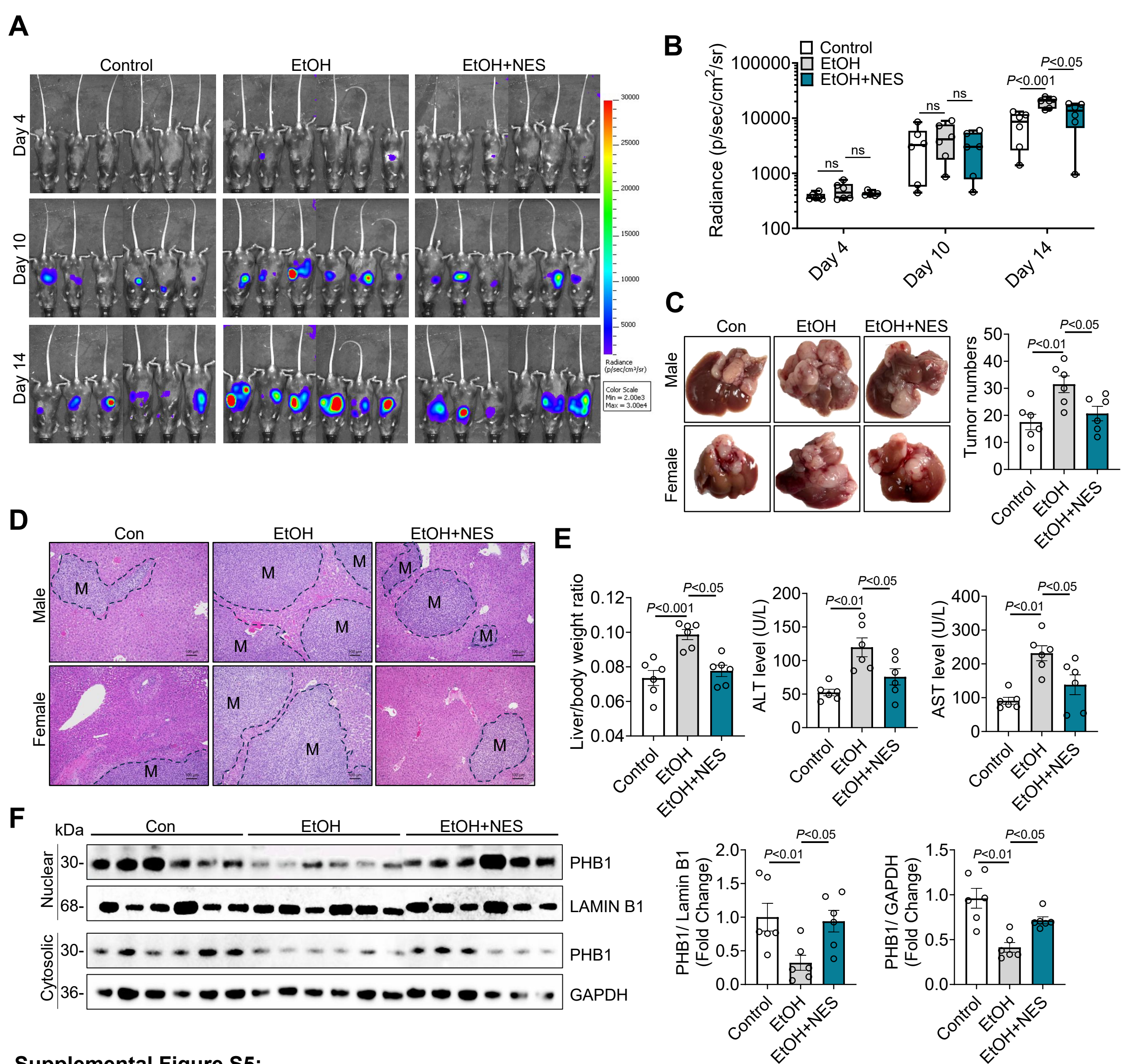
NES5 and NES10 represent 10 mg/kg and 20 mg/kg of body weight doses of NES. Data are presented as mean $\pm$ SEM. Statistical significance was assessed by one-way ANOVA with Tukey's post-hoc correction. Significance is denoted with $P<0.05$, $P<0.01$, and $P<0.001$ and ns represents not significant.



Supplemental Figure S4:

- (A) mRNA expression of *Gclc* and *Gclm* in liver of control and EtOH-fed mice with or without NES treatment (n=6).
- (B) mRNA expression of *GCLC* and *GCLM* in AH datasets GSE142530 and GSE155907 (n≥15).
- (C) mRNA expression of *Myc*, *Maf* and *Mafg* in liver of control and EtOH-fed mice with or without NES treatment (n=6).
- (D) mRNA expression of *MYC*, *MAF* and *MAFG* in AH datasets GSE142530 and GSE155907 (n≥15).

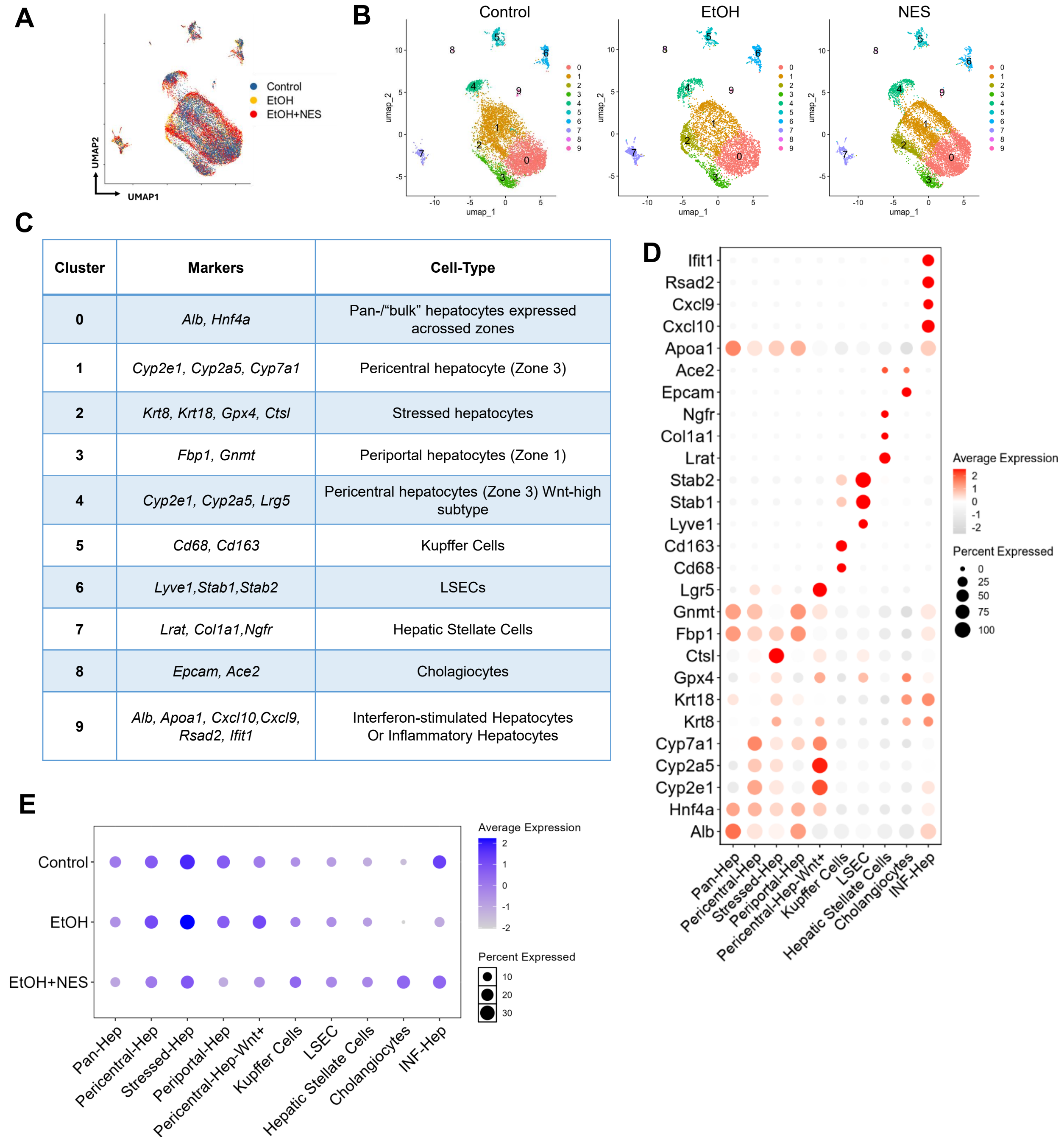
NES5 and NES10 represent 10 mg/kg and 20 mg/kg of body weight doses of NES. Data are presented as mean±SEM. Comparisons between two groups were conducted using an unpaired Student's t-test, whilst multiple group comparisons were assessed using one-way ANOVA, followed by Tukey's post hoc test. Significance is denoted with $P<0.05$, $P<0.01$, and $P<0.001$ and ns represents not significant.



Supplemental Figure S5:

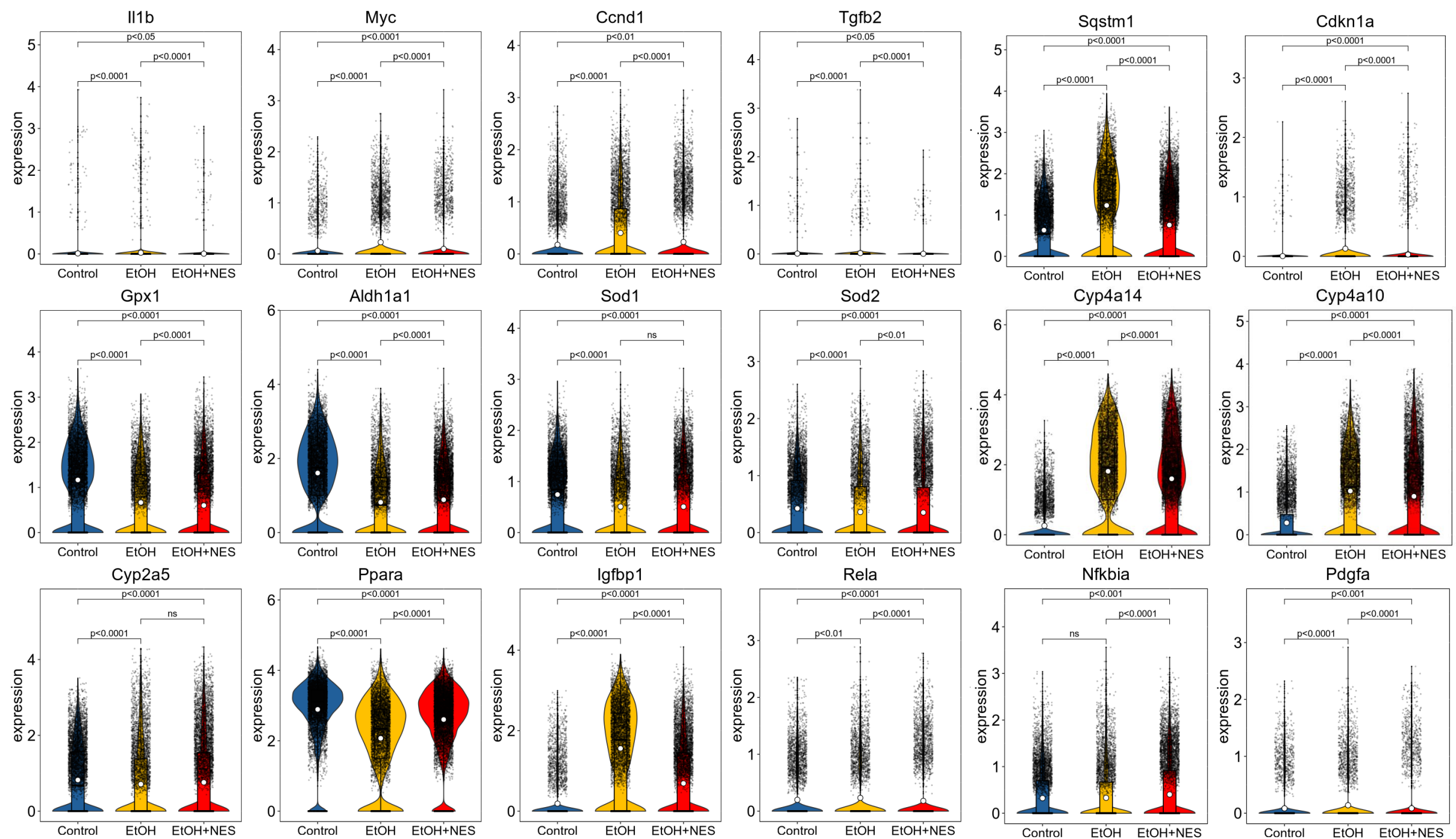
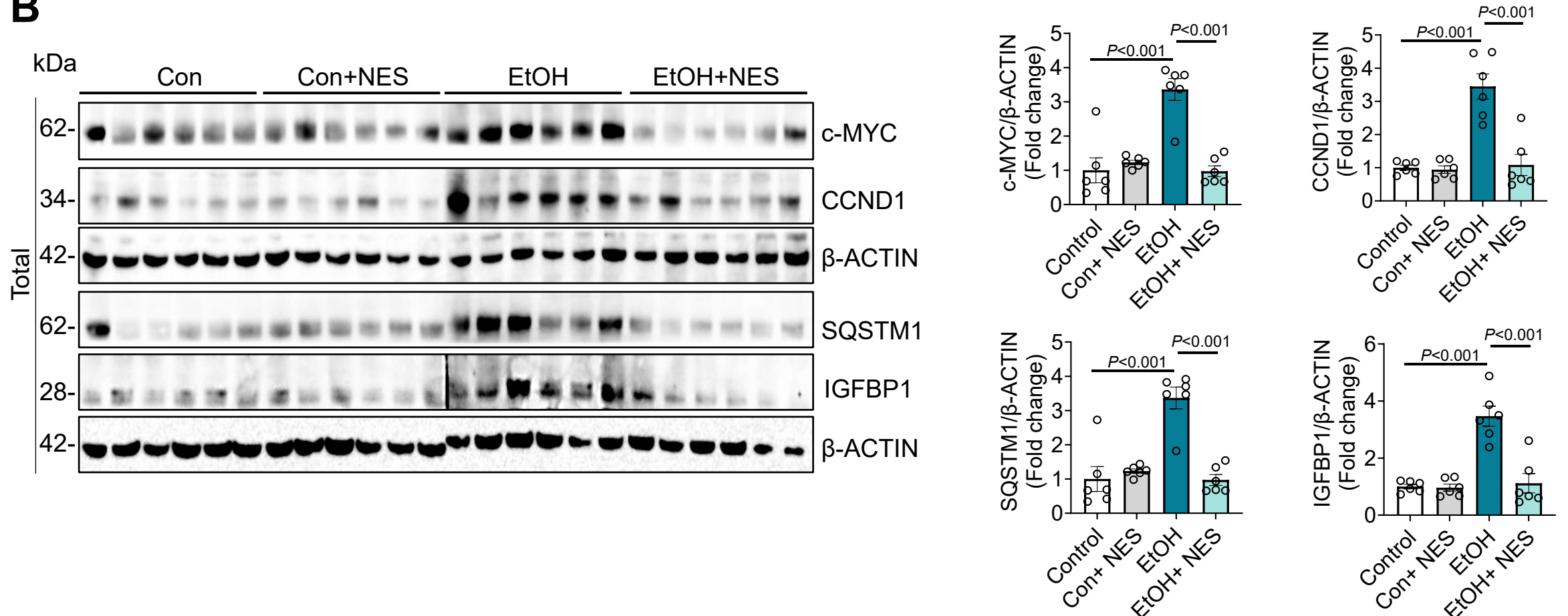
- (A) Representative in vivo bioluminescent images of control and EtOH-fed mice treated with vehicle or NES at days 4, 10, and 14 after intrasplenic injection of luciferase-expressing MC38 cells. The color bar indicates radiance (p/sec/cm²/sr) (n=6).
- (B) Box-and-whisker plots of tumor radiance for the four groups at the indicated time points (n=6).
- (C) Representative gross images of the tumor burden and quantification of tumor numbers per mouse (n=6).
- (D) H&E-stained liver sections showing metastatic lesions; scale bars, 100 µm.
- (E) Liver to body weight ratio, plasma ALT and AST levels (n=6).
- (F) Immunoblots of nuclear and cytosolic PHB1. Densitometric analyses of immunoblots are shown to the right of the blots. Samples from EtOH+NES were run on separate gels but were transferred to one membrane prior to development.

Data are presented as mean $\pm$ SEM. Statistical significance was assessed by one-way ANOVA with Tukey's post-hoc correction. Significance is denoted with $P<0.05$, $P<0.01$, and $P<0.001$.



Supplemental Figure S6

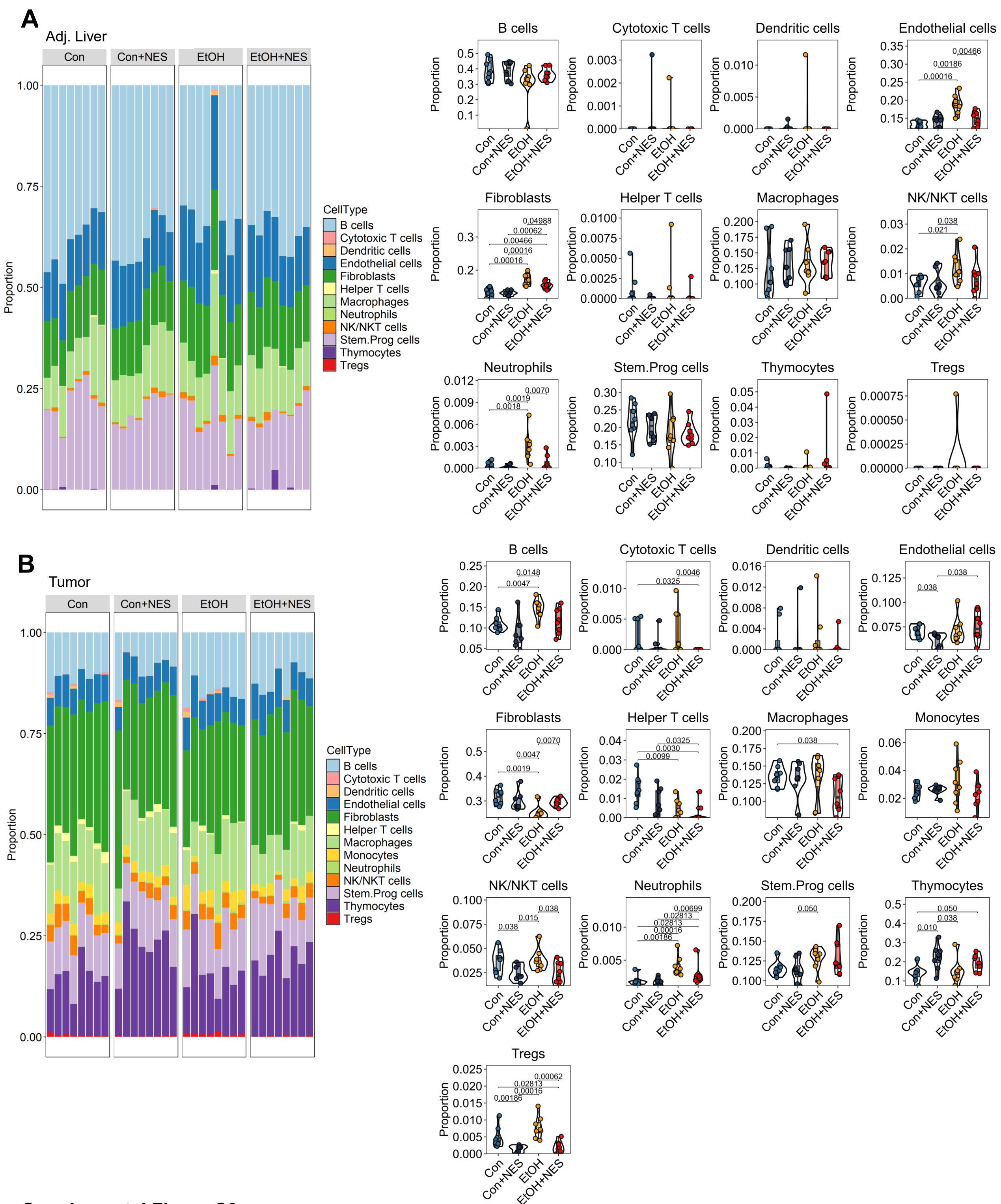
- (A) UMAP distribution of samples.
- (B) UMAP distribution of clusters in Control, EtOH and EtOH+NES group.
- (C) Marker based identification of cell-type.
- (D) Expression of marker genes was visualized using Bubble plot across different cell-types.
- (E) *Phb1* mRNA expression in different cell types.

A**B****Supplemental Figure S7:**

(A) Expression of antioxidant, inflammatory and tumorigenic genes highlighted in Figure 7E visualized using violin plots across conditions (Control, EtOH, EtOH+NES). Statistical significance was assessed using Wilcoxon rank-sum tests.

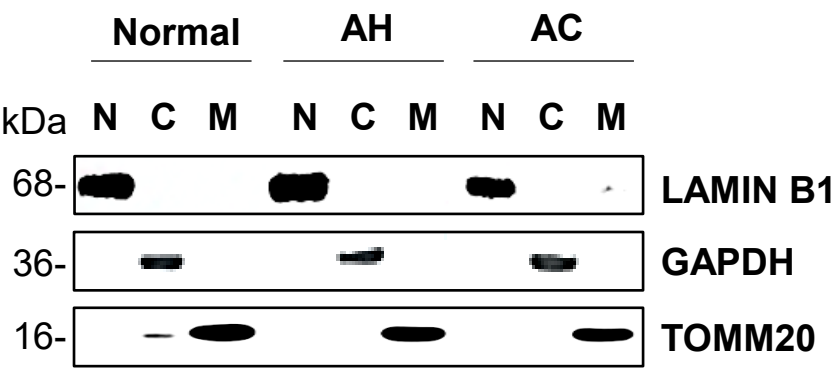
(B) Immunoblot images of Total c-MYC, CCND1, SQSTM1 and IGFBP1; β -ACTIN was used as loading control. Quantification (right) shows fold changes relative to control (n=6). Statistical significance was assessed by one-way ANOVA with Tukey's post-hoc correction.

Significance is denoted with $P < 0.01$, and $P < 0.001$.

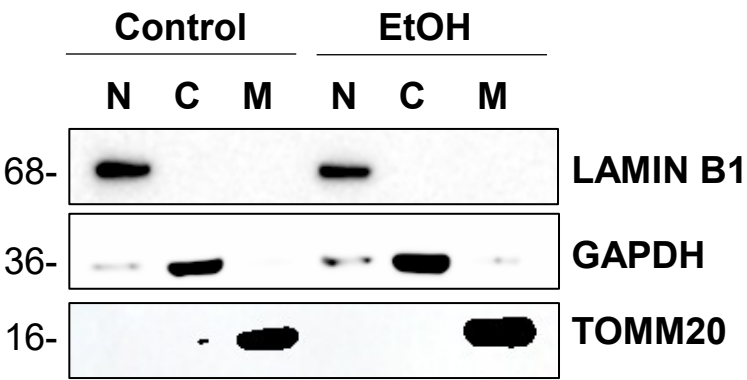


Supplemental Figure S8

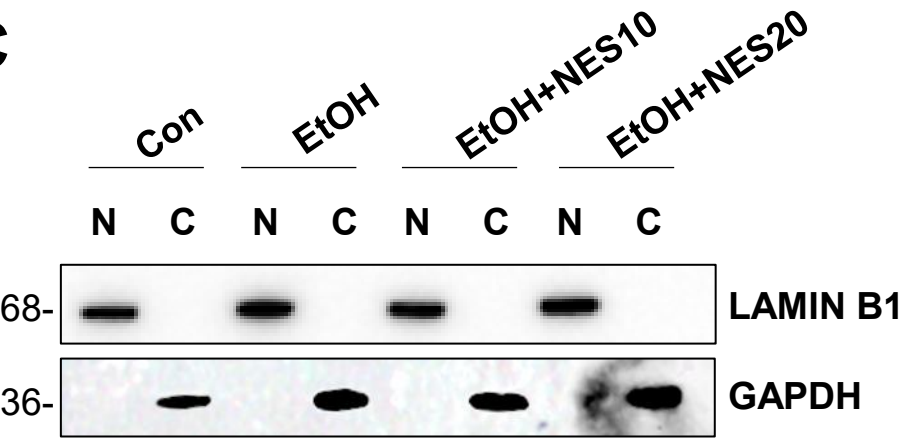
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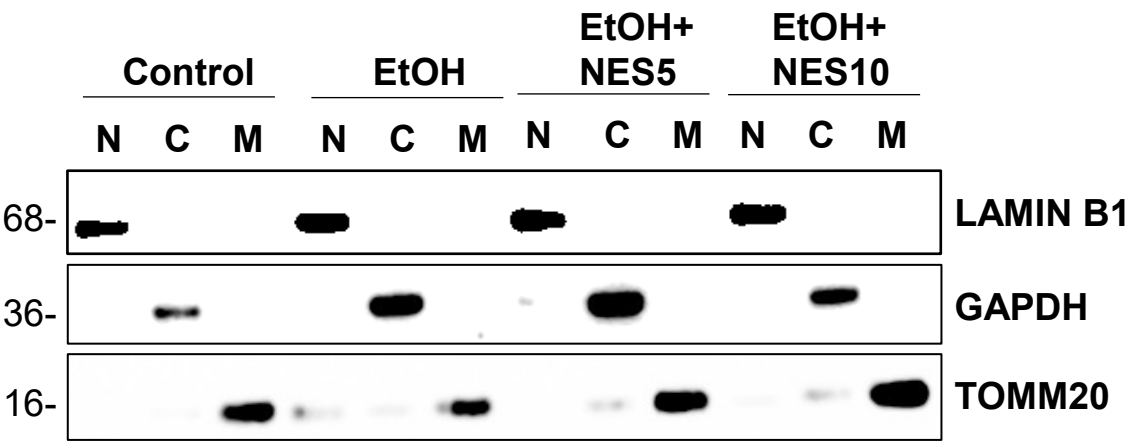
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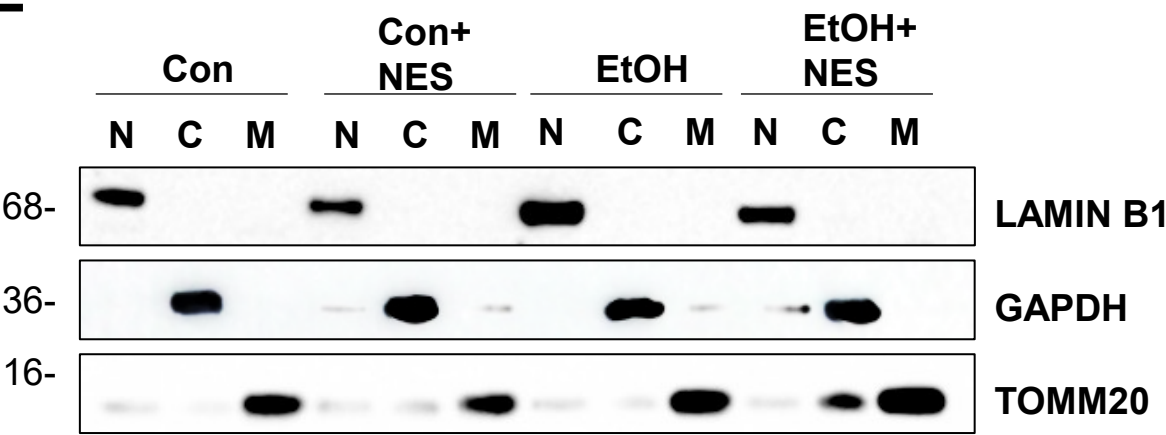
C



D



E



Supplemental Figure S9:

- (A) Nuclear, cytosolic and mitochondrial fraction enrichment blot for normal, AH and AC samples from Figure 1A and Supplemental Figure S1A.
- (B) Nuclear, cytosolic and mitochondrial fraction enrichment blot for Figure 1D.
- (C) Nuclear and fraction enrichment blot for Figure 2E.
- (D) Nuclear, cytosolic and mitochondrial fraction enrichment blot for Figure 5A.
- (E) Nuclear, cytosolic and mitochondrial fraction enrichment blot for Figure 7H.
- N,C and M represents nuclear, cytosolic and mitochondrial fractions, respectively.