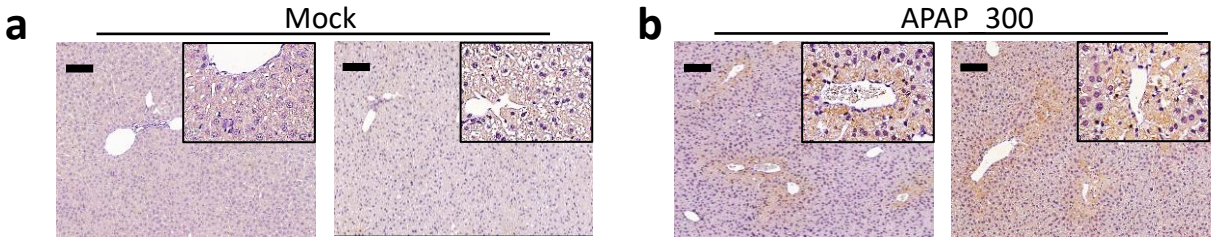
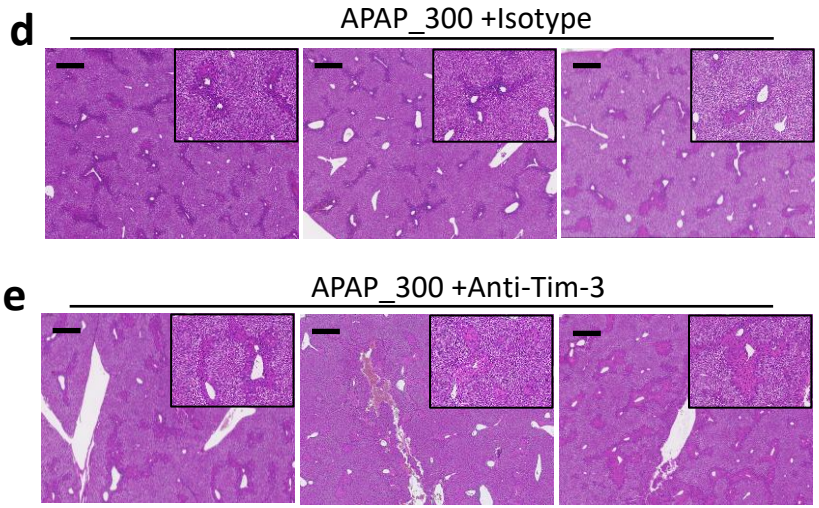
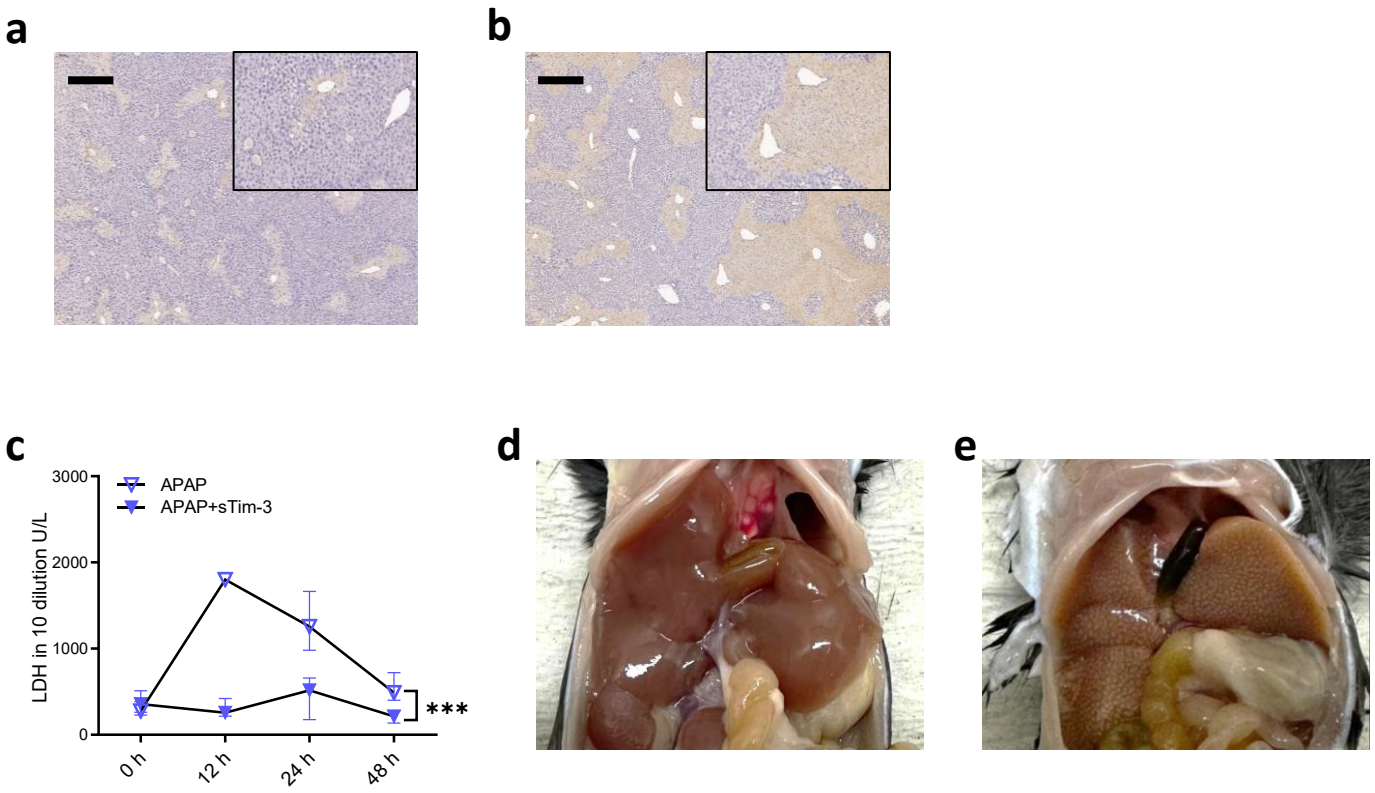


c

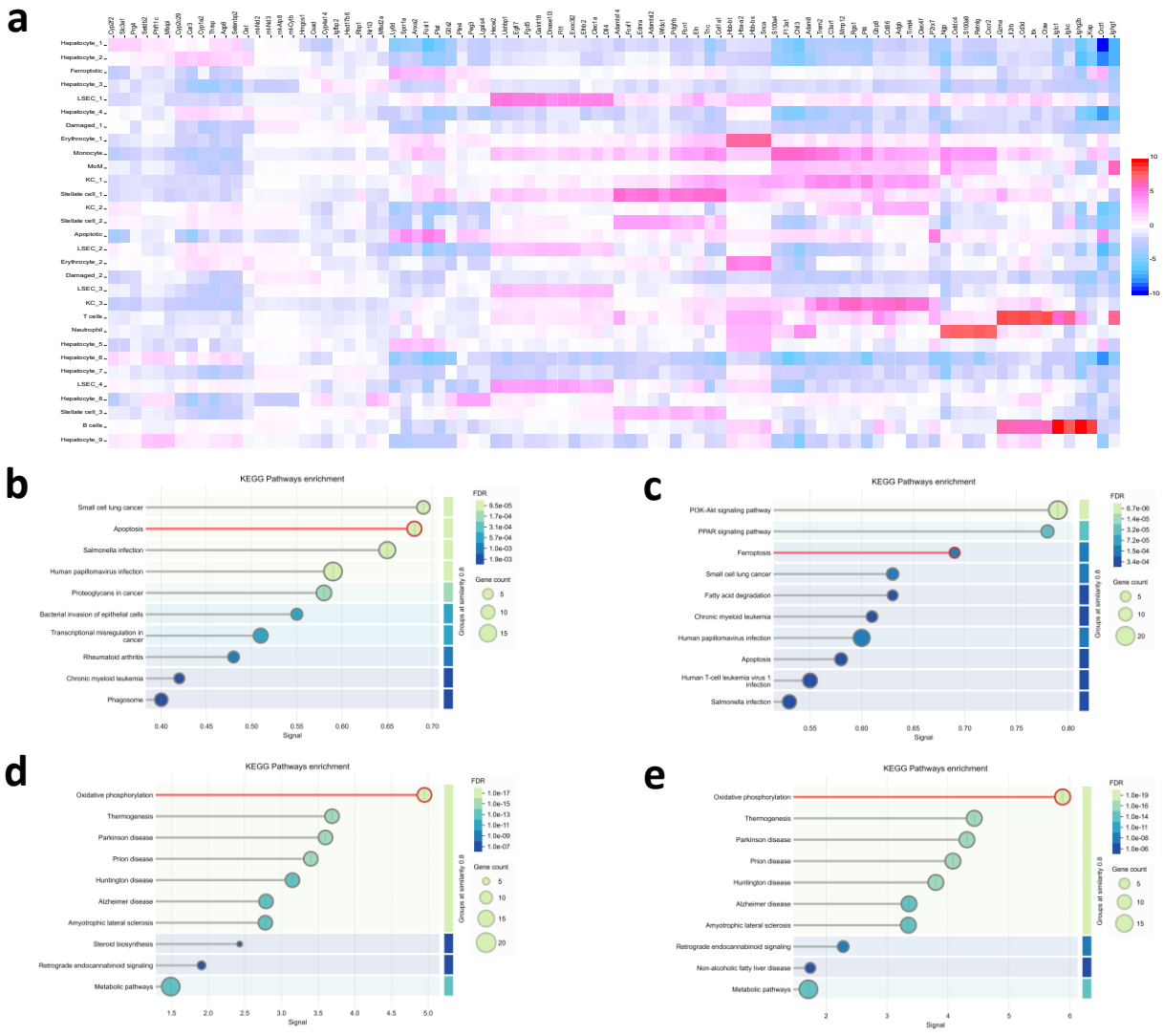
Inference Score	
135.82	Weight Loss
134.07	Chemical and Drug Induced Liver Injury
131.71	Inflammation
124.85	Necrosis
110.51	Prenatal Exposure Delayed Effects
110.21	Fibrosis
108.44	Learning Disabilities
104.89	Lung Injury
104.76	Hepatomegaly
101.87	Kidney Diseases
100.37	Memory Disorders
96.73	Hyperplasia
92.66	Acute Kidney Injury
92.4	Weight Gain
91.42	Cognition Disorders
88.41	Testicular Diseases
87.57	Nerve Degeneration
84.85	Edema
83.82	Lung Diseases
83.34	Birth Weight



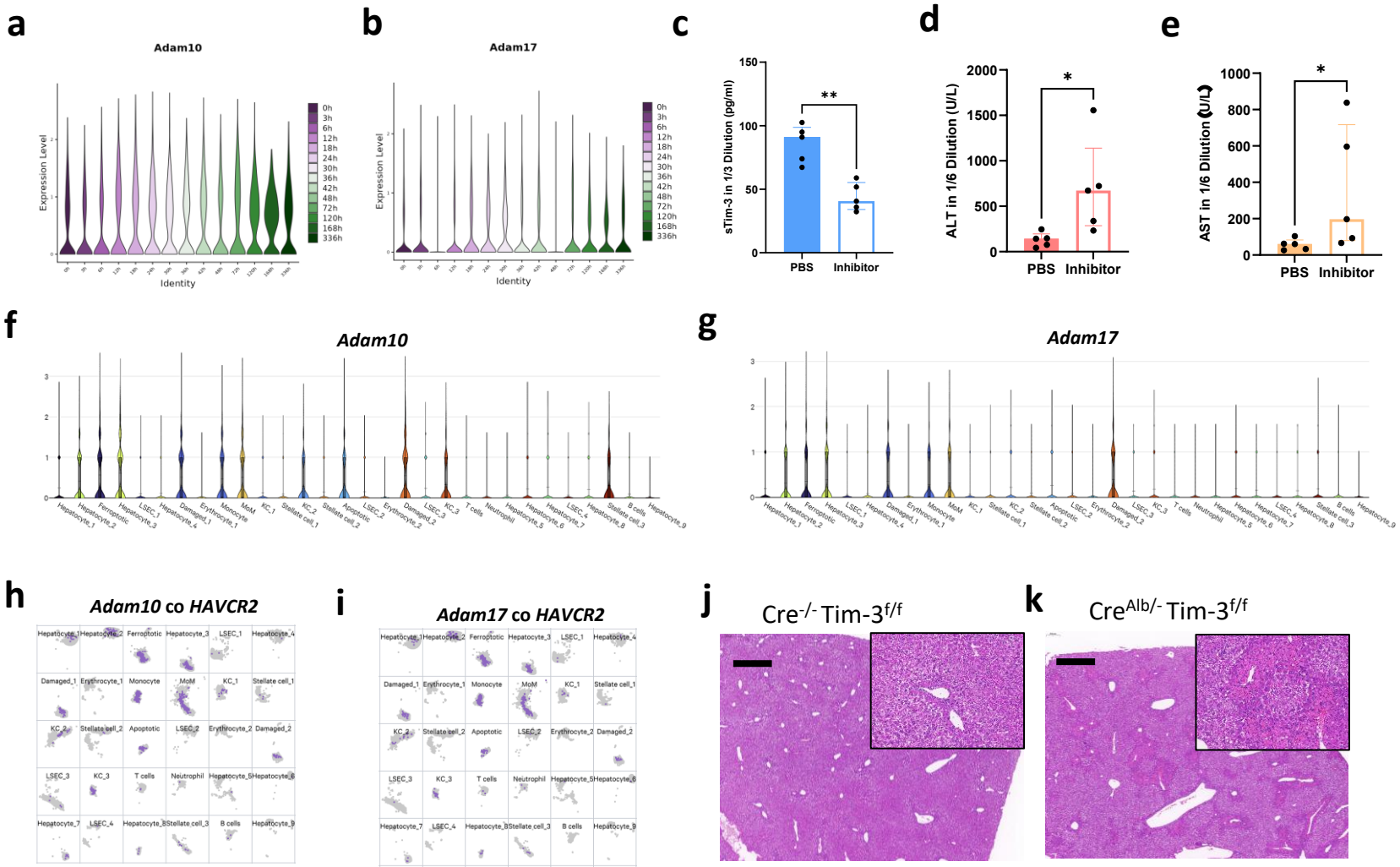
Supplementary Fig. 1 Contribution of Tim-3 in drug-induced liver injury. **a**, **b** Immunohistochemical staining of Tim-3 in untreated (**a**) and APAP-administered (**b**) mouse livers. APAP, 300 mg/kg body weight (b.wt.). Scale bar = 100 µm. **c** Analyzing inference score between diseases and Tim-3 expression in Comparative Toxicogenomics Database. **d**, **e** HE staining of liver from control (**d**) and anti-Tim-3 antibody-treated (**e**) mice (*n* = 3). Scale bar = 400 µm. The experiments were replicated three times (**a**, **b**, **d**, **e**).



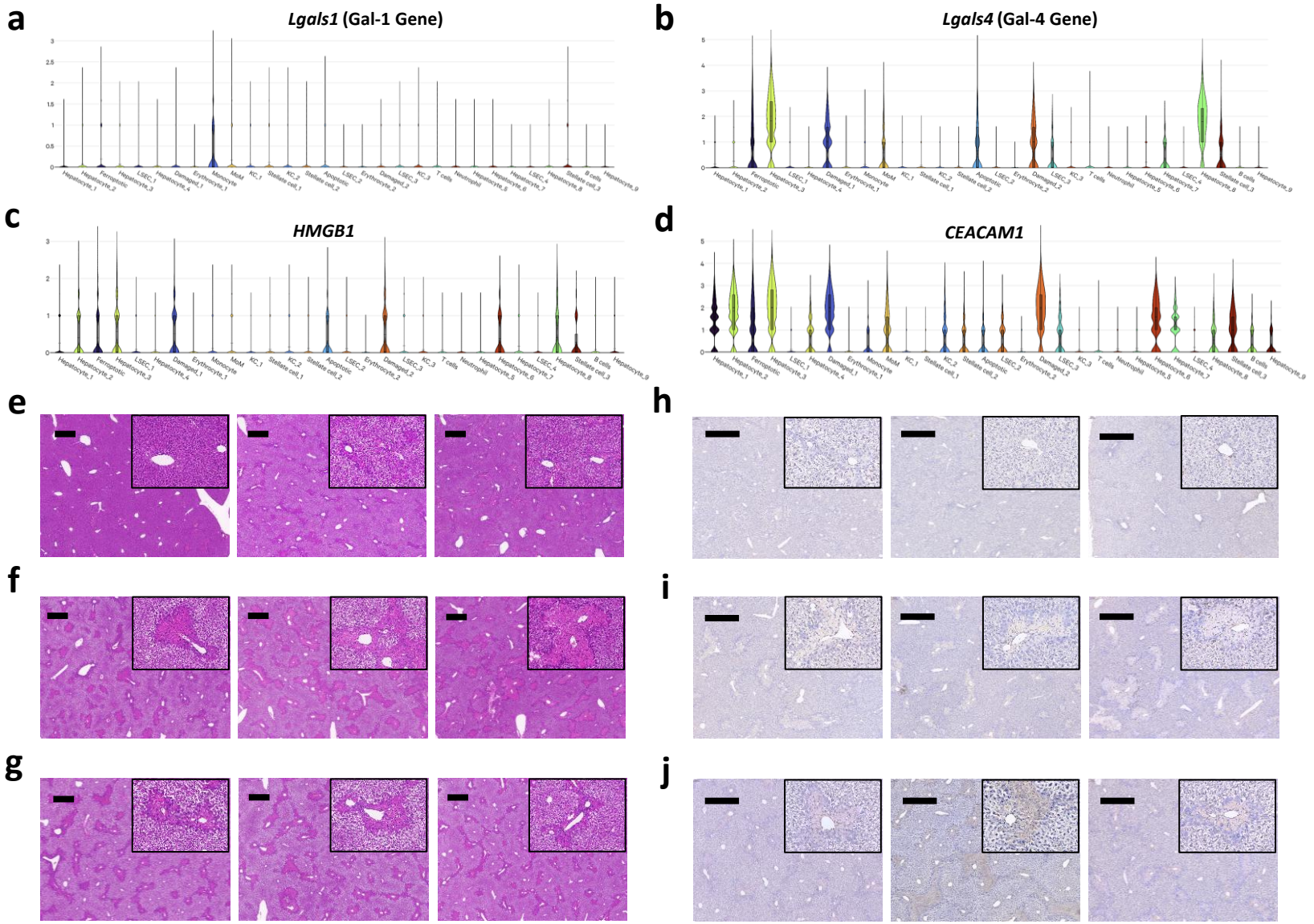
Supplementary Fig. 2 Function of exogenous sTim-3 in APAP-administrated mice. **a**, **b** TUNEL staining of liver from APAP-administered (600 mg/kg b.wt.) mice treated with 200 μg sTim-3 (**a**) or untreated control (**b**). Scale bar = 300 μm. **c** Dynamic monitor the fluctuations of LDH in APAP-administered (300 mg/kg b.wt.) mice with or without 200μg sTim-3. *n* = 5. **d**, **e** Visible changes of livers between mice treated with 200 μg sTim-3 (**d**) or untreated control (**e**). Significance was calculated by two-way ANOVA test. Graphs were showing with median with the interquartile range. The experiments were replicated three (**a**, **b**) or five times (**c**-**e**). *P < 0.05, **P < 0.01, ***P < 0.001.



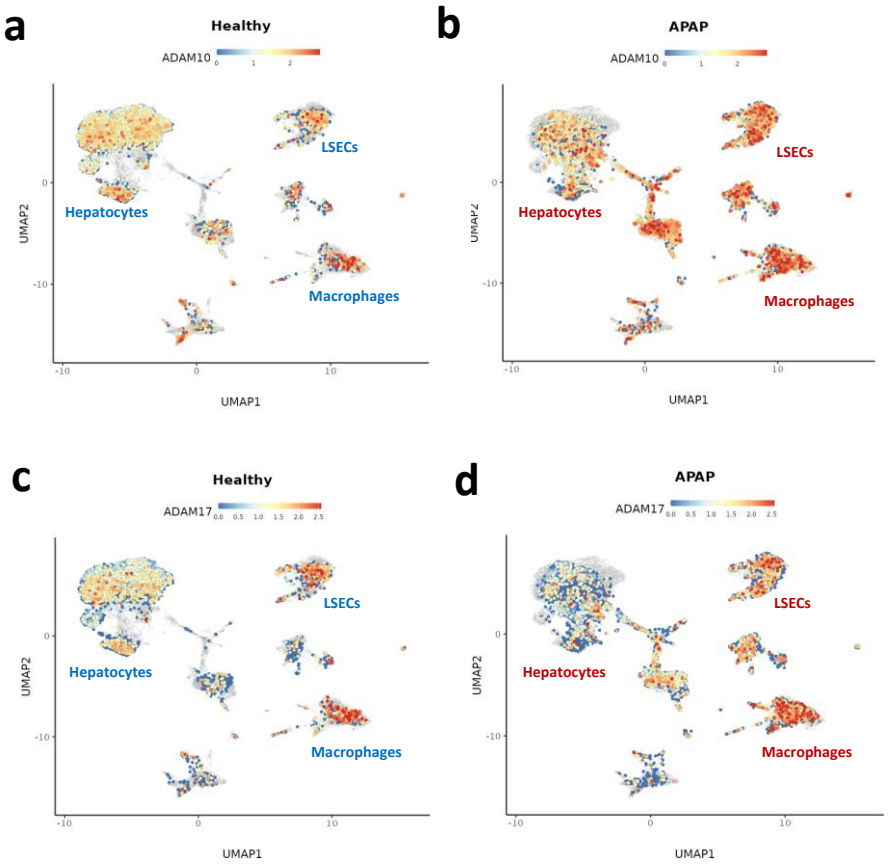
Supplementary Fig. 3 snRNA sequence of sTim-3-treated mice. **a** Characteristic genes in clusters showing with heatmap graph. **b**-**e** Pathway enrichment in apoptotic (**b**), ferroptotic (**c**) and two damaged clusters (**d**, **e**).



Supplementary Fig. 4 Protective effect of hepatocyte-derived Tim-3 on liver injury. **a**, **b** Analysis levels of ADAM10 (**a**) and ADAM17 (**b**) in mice treated with APAP. **c**-**e** Detection of serum sTim-3 (**c**), ALT (**d**) and AST (**e**) levels in APAP-administrated mice treated with an ADAM10/17 inhibitor, INCB3619. *n* = 5. **f**, **g** Expression distribution of ADAM10 (**f**) and ADAM17 (**g**) in clusters from snRNA sequence. **h** Co-expression of ADAM10 and Tim-3 gene (*HAVCR2*). **i** Co-expression of ADAM17 and Tim-3 gene (*HAVCR2*). **j**, **k** HE staining liver tissues from the HAVCR2 conditional knockout mouse (**j**) and its littermate (**k**). Scale bar = 500 μm. Significances were calculated by the Mann-Whitney test. Graphs were showing with median with the interquartile range. The experiments were replicated three times (**c**-**e**, **j**, **k**). *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$



Supplementary Fig. 5 The downstream ligands involved in exogenous sTim-3 protection. **a**-**d** Expression distribution of Gal-1 (**a**), Gal-4 (**b**), HMGB1 (**c**) and CAECAM1 (**d**) in clusters from snRNA sequence. **e**-**g** HE staining liver tissues from three exogenous sTim-3 treated mice (**e**) with anti-Gal-9 antibody (**f**) or anti-Gal-3 antibody (**g**), *n* = 3. Scale bar = 500 μm. **h**-**j** TUNEL staining liver tissues from three exogenous sTim-3 treated mice (**h**) with anti-Gal-9 antibody (**i**) or anti-Gal-3 antibody (**j**), *n* = 3. Scale bar = 400 μm. The experiments were replicated three



Supplementary Fig. 6 Analyzing levels of ADAM10/17 in clinical samples. **a**, **b** Analysis of ADAM10 gene expression in snRNA-seq from Healthy (**a**) and APAP-induced ALF (**b**). **c**, **d** Analysis of ADAM17 gene expression in snRNA-seq from Healthy (**c**) and APAP-induced ALF (**d**).