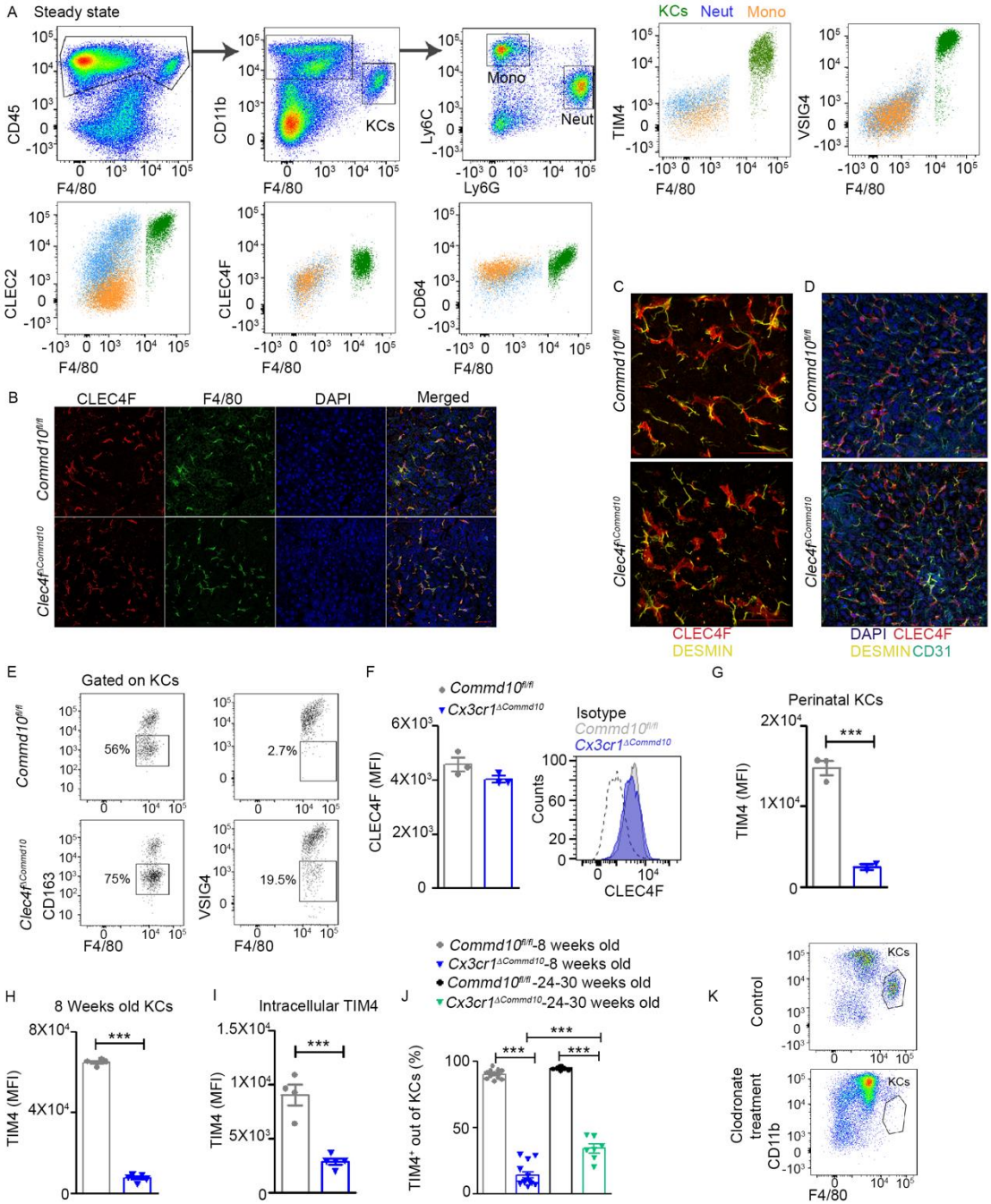


**Figure S1: *Clec4f*$^{\Delta Commd10}$ KCs fit into the KC niche, but are being replaced by MoKCs; related to Figure 1.** (A) Representative flow cytometry images displaying gating strategy used to define KCs and infiltrating Ly6C$^{hi}$ monocytes and neutrophils in the healthy liver. (B-D) Representative confocal microscopy images obtained from liver sections of *Commd10*$^{fl/fl}$ and *Clec4f*$^{\Delta Commd10}$. (B) Expression of Clec4F (red), F4/80 (green) and nuclei (blue), original magnification: ×20. Bars= 100µm. (C) Expression of Clec4F (red) and desmin (yellow), original magnification: ×40. Bars=200 µm. (D) Expression of Clec4F (red) and desmin (yellow), CD31 (cyan) and nuclei (blue). Original magnification: ×20. Bars= 100µm. (E) Representative flow cytometry plots displaying the representation of CD163$^{-}$ and VSIG4$^{-}$ among *Commd10*$^{fl/fl}$ and *Clec4f*$^{\Delta Commd10}$ KCs. (F) Left, mean fluorescence intensity (MFI) of CLEC4F. Right, representative histogram plot showing expression of CLEC4F on *Commd10*$^{fl/fl}$ and *Cx3cr1*$^{\Delta Commd10}$ KCs, in comparison to isotype control (dashed black line) (n=3). (G-I) mean fluorescence intensity (MFI) of TIM4 expression in KCs from (G) perinatal mice, (H), eight weeks old mice, and (I) intracellular staining of TIM4 in KCs. (G-I: n≥3) (J) Frequency of TIM4$^{+}$ cells among KCs from eight and 24-30 weeks old *Commd10*$^{fl/fl}$ and *Cx3cr1*$^{\Delta Commd10}$ mice (n>5). (K) Representative flow cytometry plots showing depletion of KC following clodronate liposome treatment. Data were analyzed by unpaired, two-tailed *t*-test and are presented as mean ± SEM with significance: ***$p < 0.001$. Experiments were repeated at least 3 times (A-F), twice (H, J) or once(G, I, K).

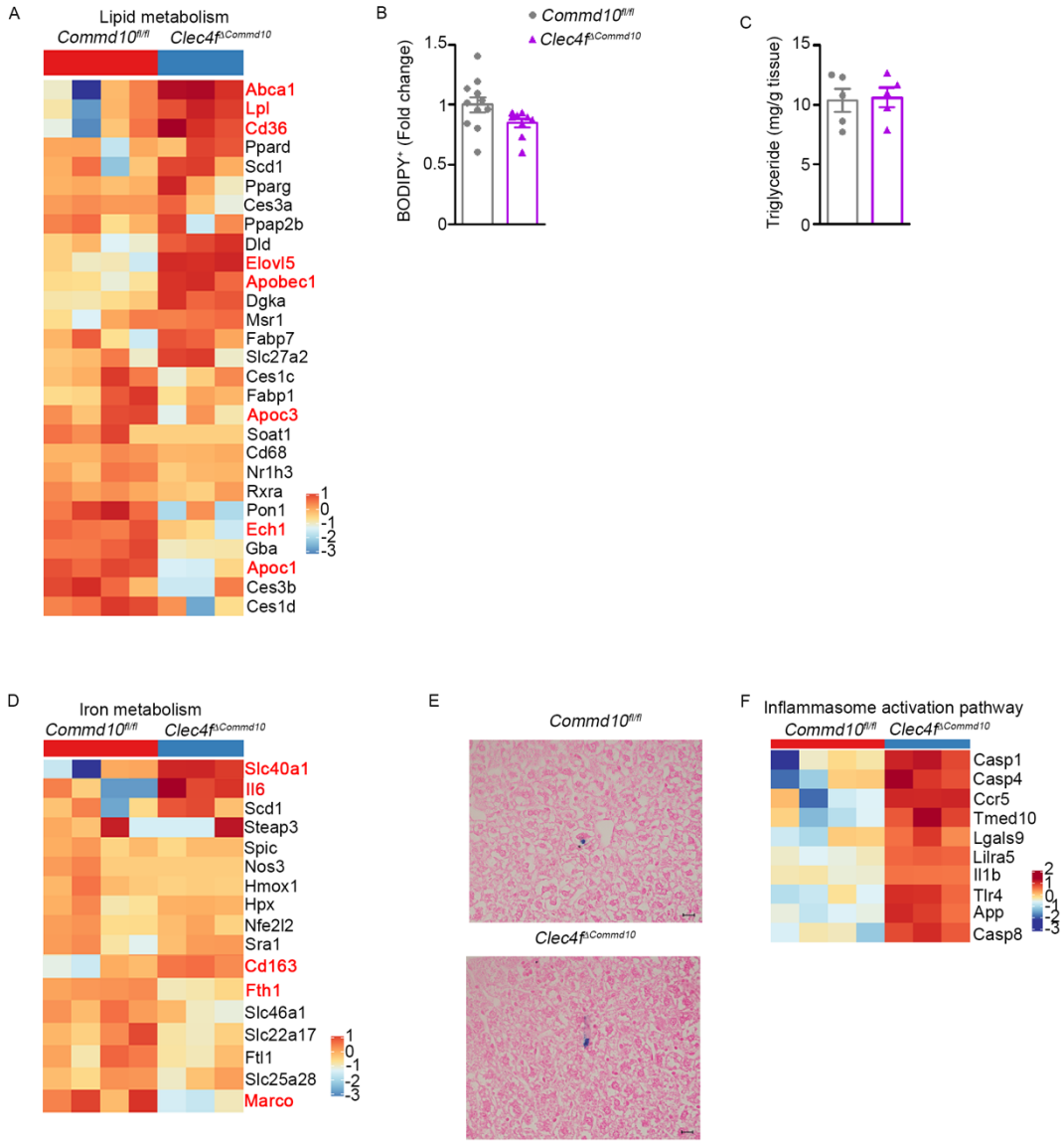


**Figure S2: COMMD10-deficient KCs acquire liver-specific functional KC identity; related to Figure 2.**
(A) MARS-RNAseq heat map analysis displaying expression of genes associated with lipid metabolism in *Commd10*$^{fl/fl}$ versus *Clec4f*$^{\Delta Commd10}$ KCs. (B) Neutral lipid content of *Commd10*$^{fl/fl}$ and *Clec4f*$^{\Delta Commd10}$ steady state KCs. Results shown are mean fluorescence intensity (MFI) for BODIPY staining (n>10). (C) Triglycerides levels normalized to liver tissue mass in *Commd10*$^{fl/fl}$ and *Clec4f*$^{\Delta Commd10}$ livers (n=5). (D) MARS-RNAseq heat map analysis displaying expression of genes associated with iron metabolism in *Commd10*$^{fl/fl}$ versus *Clec4f*$^{\Delta Commd10}$ KCs. (E) Representative images of Perl's iron, with Prussian blue reaction staining of *Commd10*$^{fl/fl}$ and *Clec4f*$^{\Delta Commd10}$ liver sections. Original magnification= x4. Bars=50µm. (F) MARS-RNAseq heat map analysis of *Commd10*$^{fl/fl}$ versus *Clec4f*$^{\Delta Commd10}$ KCs displaying variance of genes associated with inflammasome activation pathway. For A and D, significantly differentially expressed genes are marked red. Analysis was performed on differentially expressed genes (n>3, $p < 0.05$; raw P values were adjusted for multiple testing using the procedure of Benjamini and Hochberg, ≥1.5-fold change).

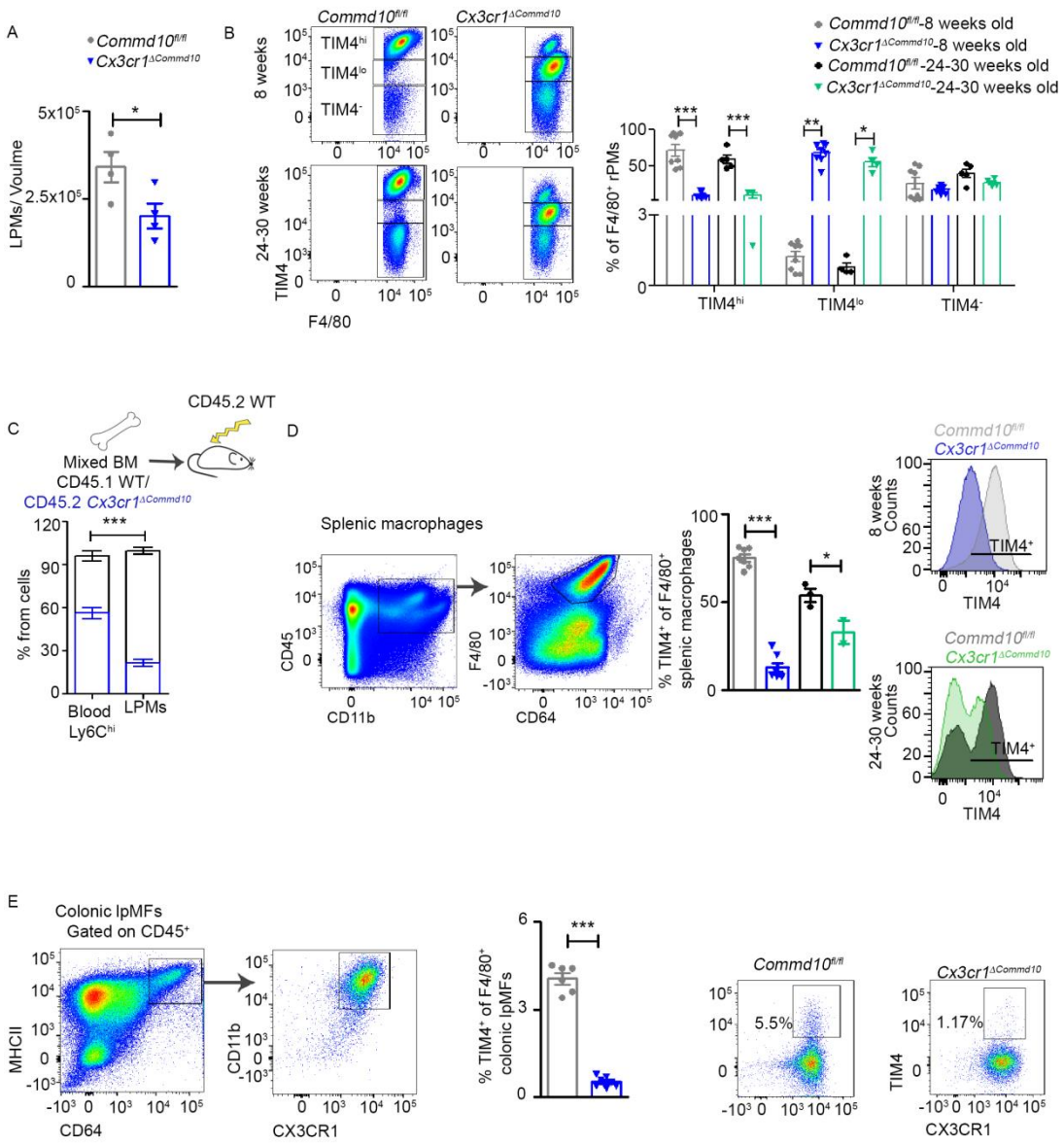


**Figure S3: COMMD10 is crucial for the homeostatic maintenance of resident macrophages of the peritoneum, spleen and gut; related to Figure 3.**

(A) LPMs counts normalized to extracted volume of peritoneal lavage in *Commd10*$^{fl/fl}$ and *Cx3cr1*$^{\Delta Commd10}$ mice (n=4). (B) Quantification of TIM4$^{+}$, TIM4$^{lo}$ and TIM4$^{-}$ LPMs frequency among total LPMs from *Commd10*$^{fl/fl}$ and *Cx3cr1*$^{\Delta Commd10}$ mice (n≥4). (C) quantification of % chimerism in blood Ly6C$^{hi}$ monocytes and LPMs assessed in mixed CD45.1 WT/ CD45.2 *Cx3cr1*$^{\Delta Commd10}$ BM chimeras at eight weeks post irradiation (n≥8). (D) Left, frequency of TIM4$^{+}$ among splenic macrophages in eight versus 24-30 weeks old *Commd10*$^{fl/fl}$ and *Cx3cr1*$^{\Delta Commd10}$ mice. Right, representative histogram plot showing expression level of TIM4. (E) Left, frequency of TIM4$^{+}$ among colonic lamina propria macrophages (lpMFs) in eight weeks old *Commd10*$^{fl/fl}$ and *Cx3cr1*$^{\Delta Commd10}$ mice. Right, representative flow cytometry plot showing expression level of TIM4 in lpMFs (24-30 weeks: n>2, eight weeks n=4). Data were analyzed by unpaired, two-tailed *t*-test and are presented as mean ± SEM with significance: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. Experiments were repeated twice (B, C, D, E) or once (A).

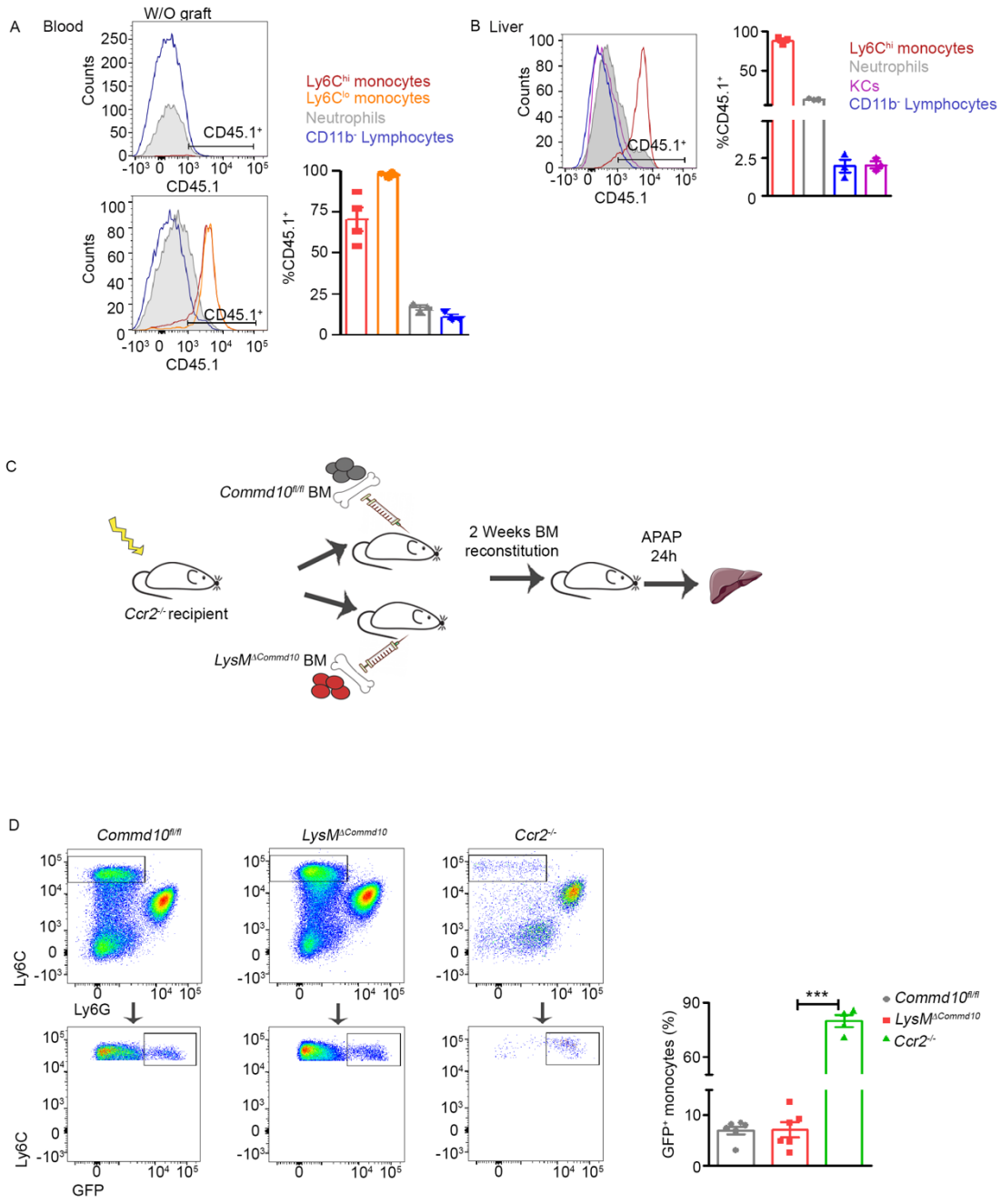


**Figure S4: COMMD10 is important for tuning the inflammatory activity of Ly6C$^{hi}$ monocytes in acetaminophen-induced liver injury (AILI); related to Figure 5.** Irradiated (3 Gy) *Cx3cr1$^{gfp/+}$Ccr2$^{-/-}$* mice were engrafted with CD45.1 congenic BM, allowed to reconstitute for two weeks, and then subjected to AILI 24 h (n>4). (A- B) Representative flow cytometry images illustrating the chimerism (% of CD45.1$^{+}$) obtained in (A) blood and (B) liver in indicated immune cells. (C) Schematic illustration of the experimental design: irradiated (3 Gy) *Cx3cr1$^{gfp/+}$Ccr2$^{-/-}$* mice were engrafted with BM from *LysM$^{\Delta Commd10}$* or *Commd10$^{fl/fl}$* littermate mice. Two weeks post reconstitution, mice were subjected to AILI 24 h. (D) Representative flow cytometry images illustrating the chimerism obtained in liver Ly6C$^{hi}$ monocytes marked by their negative expression of CX3CR1-GFP reporter protein. Data were analyzed by unpaired, two-tailed t-test and are presented as mean ± SEM with significance: ***p< 0.001. Data are representative three independent experiments.

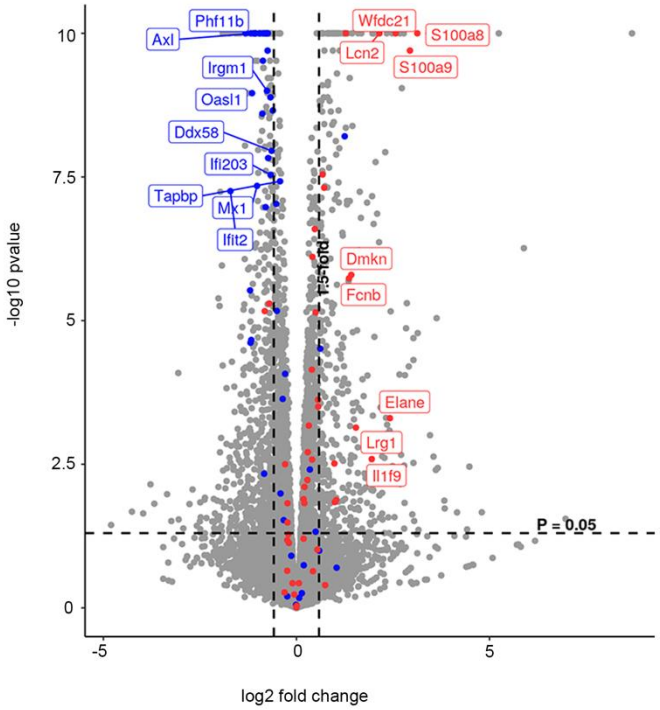


**Figure S5: COMMD10-deficient Ly6C$^{hi}$ monocytes display higher expression of 'neutrophil-like' monocyte (NeuMo) signature genes; related to Figure 6.** Volcano plots comparing *Commd10$^{fl/fl}$* and *LysM$^{\Delta Commd10}$* Ly6C$^{hi}$ monocytes, the expression pattern of both NeuMO and DCMo associated genes as depicted from (Weinreb et al., 2020). Analysis was performed on differentially expressed genes (n>3, $p$< 0.05; raw P values were adjusted for multiple testing using the procedure of Benjamini and Hochberg, ≥1.5-fold change).

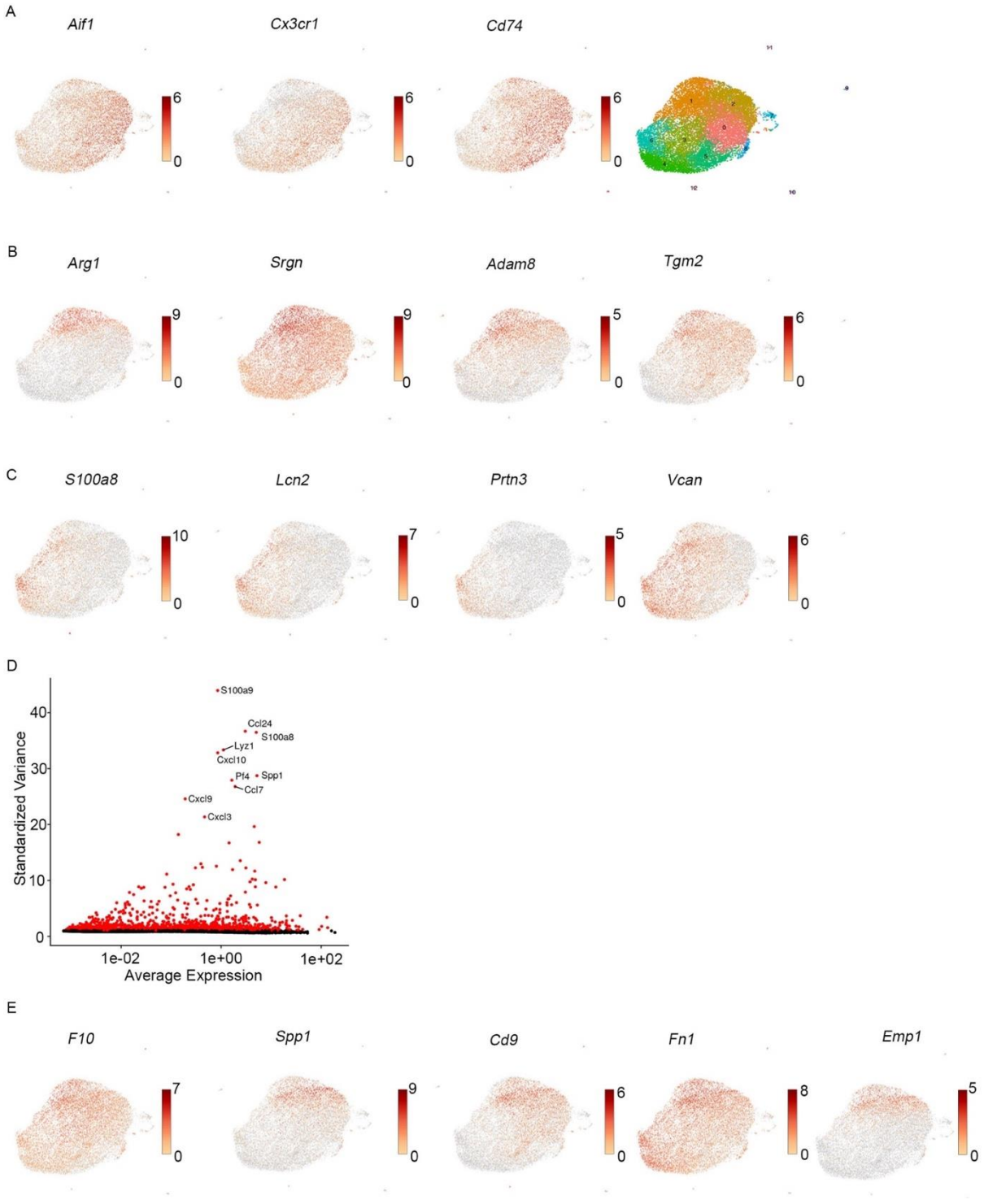


**Figure S6: COMMD10 deletion-induces a biased differentiation of Ly6C$^{hi}$ monocytes toward 'neutrophil-like' monocytes (NeuMo) and lipid associated macrophages (LAMs); related to Figure 7.** Single cell RNA-seq analysis of liver Ly6C$^{hi}$ monocytes at AILI 24 h. Gene expression domains of (A) cluster 0, (B) cluster 1, (C) NeoMo markers (D) and (E) LAM markers. Analysis was performed on differentially expressed genes ($p < 0.05$; non-parametric Wilcoxon rank sum test, ≥1.5-fold change).

| REAGENT or RESOURCE | SOURCE | IDENTIFIER |
|---|---|---|
| *Tnfa* FWD:GGTGCCTATGTCTCAGCCTCTT | Merck | N/A |
| *Tnfa* REV:GCCATAGAACTGATGAGAGGGAG | Merck | N/A |
| *Il-1b* FWD:TGGACCTTCCAGGATGAGGACA | Merck | N/A |
| *Il-1b* REV: GTTCATCTCGGAGCCTGTAGTG | Merck | N/A |
| *Cxcl1* FWD:TCCAGAGCTTGAAGGTGTTGCC | Merck | N/A |
| *Cxcl1* REV:AACCAAGGGAGCTTCAGGGTCA | Merck | N/A |
| *Cxcl2* FWD: CATCCAGAGCTTGAGTGTGACG | Merck | N/A |
| *Cxcl2* REV: GGCTTCAGGGTCAAGGCAAACT | Merck | N/A |
| *Timd4* FWD: CTACAGACAAGCCGTACTCA | Merck | N/A |
| *Timd4* REV: GTCTTCATCATCCCTCCC | Merck | N/A |
| *Ccl2* FWD: GCTACAAGAGGATCACCAGCAG | Merck | N/A |
| *Ccl2* REV: GTCTGGACCCATTCCTTCTTGG | Merck | N/A |
| *Gata6* FWD:ATGCGGTCTACAGCAAGATGA | Merck | N/A |
| *Gata6* REV: CGCCATAAGGTAGTGGTTGTGG | Merck | N/A |

**Figure S7: List of oligonucleotide sequences used for qRT-PCR; Related to Figure 1F, Figure 3B, Figure 4F, Figure 5E.**