

Figure S1

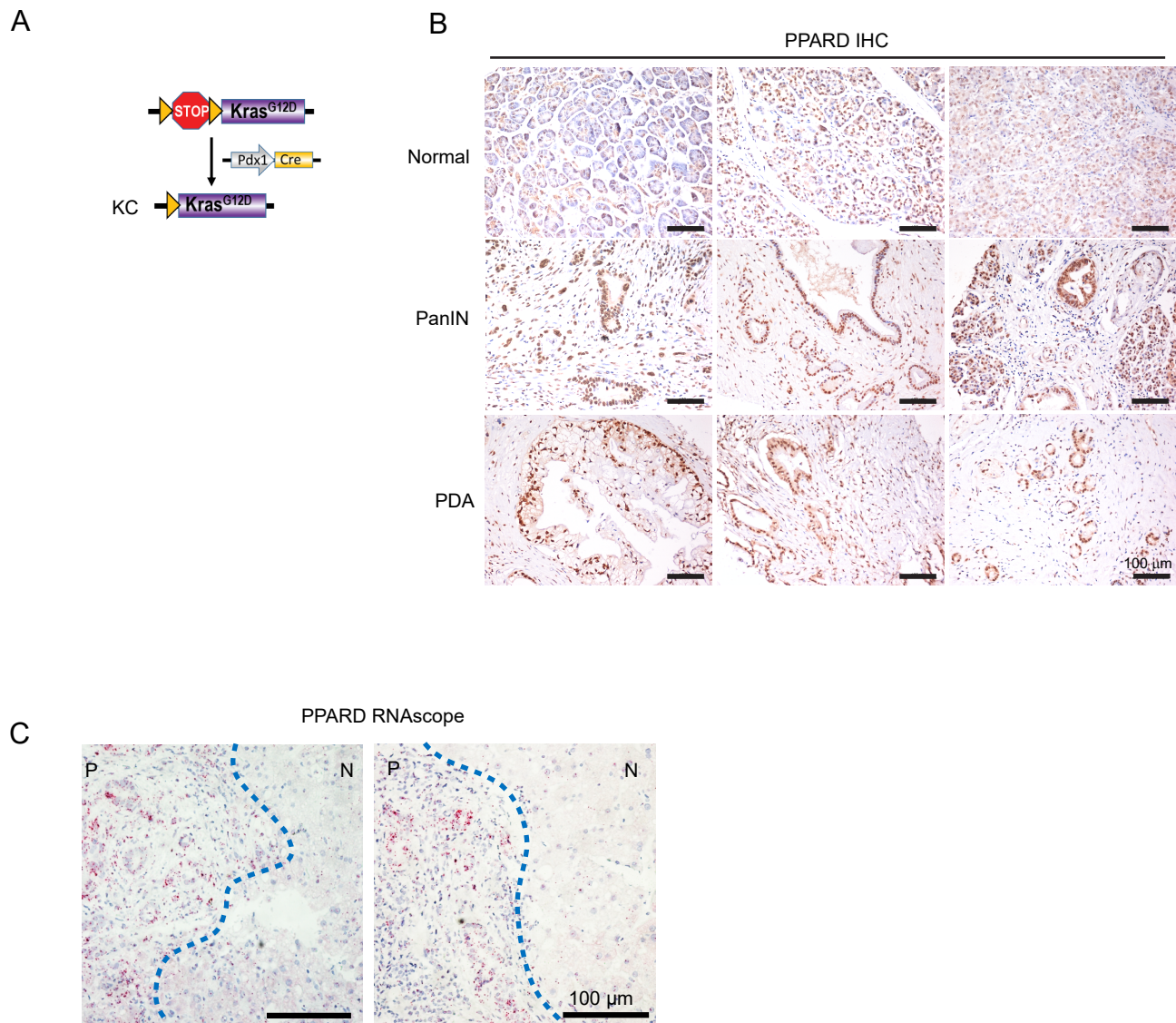


Figure S1. PPARD is upregulated in pancreatic cancer. Related to Figure 1.

(A) Schematic diagram for the generation of KC mice.

(B) Representative images of PPARD immunochemistry staining for human pancreatic tissue microarray samples with normal, PanIN, and PDAC areas.

(C) Representative images of PPARD RNAscope in situ hybridizations for human biopsied pancreatic tissue samples, including PanINs (P) and pancreatic normal areas (N).

Figure S2

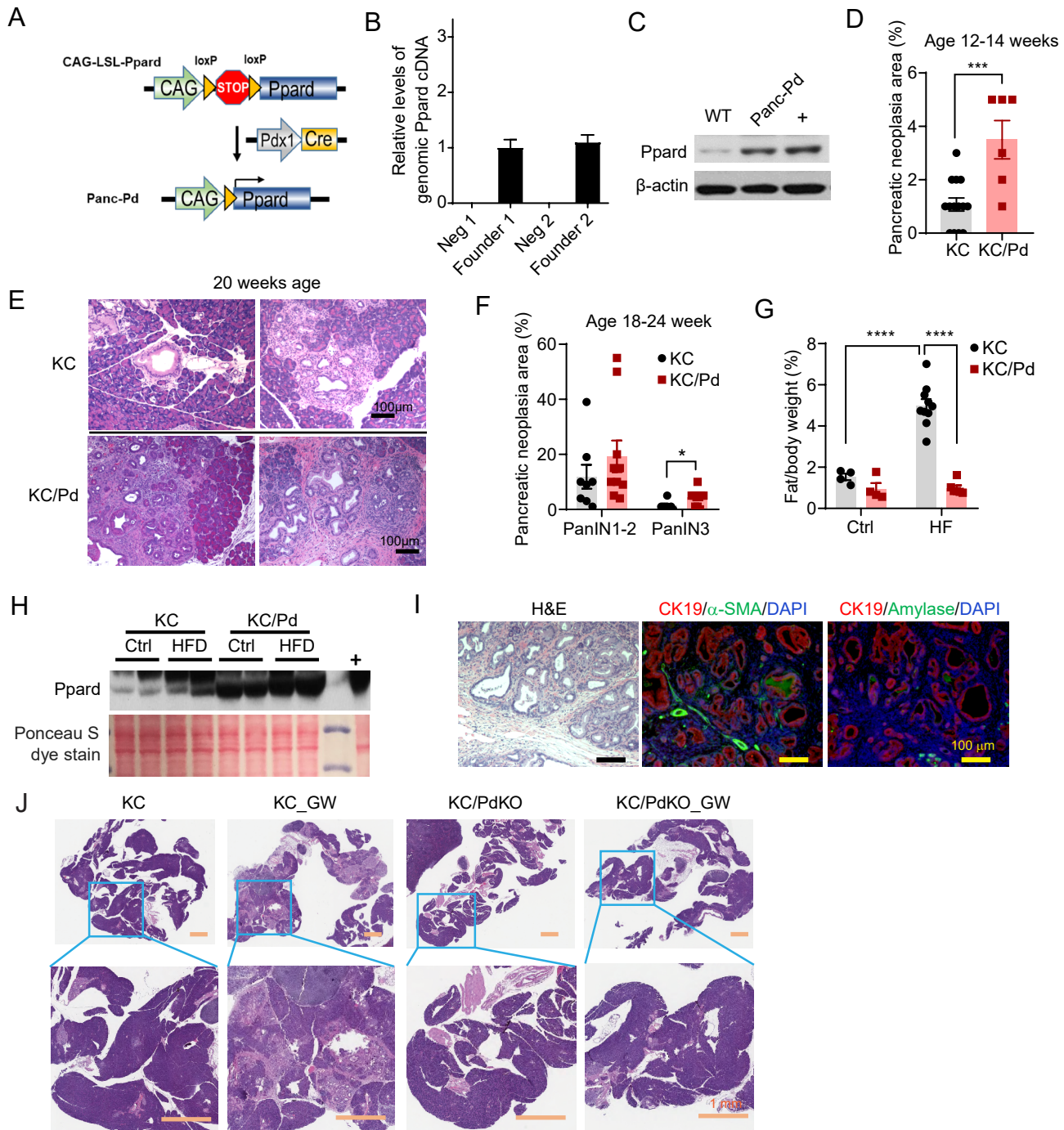


Figure S2. Hyperactivation of Ppard promotes pancreatic tumorigenesis in KC mice. Related to Figures 2 and 3.

(A) Schematic diagram of the generation of Panc-Pd mice. CAG-LSL-Ppard transgenic mice were bred with *Pdx1-Cre* mice to generate *Pdx1-Cre*, CAG-LSL-*Ppard* mice, designated as Panc-Pd mice.

(B, C) Characterization of Panc-Pd mice. The relative levels of genomic Ppard cDNA **(B)** in tails, measured by qPCR, and Ppard protein levels in mouse pancreata **(C)**, measured by Western blot in Panc-Pd mice. "+" indicates positive control of Ppard.

(D) Comparisons of percentages of pancreatic neoplasia areas between KC and KC/Pd mice at age 12-14 weeks (n=6-12 mice per group).

(E, F) Histologic characterization of the pancreata in KC and KC/Pd mice at age 20 weeks. **(E)** Representative images of H&E staining for the indicated mice are shown. **(F)** Comparisons of the percentages of pancreatic neoplastic areas shown as PanIN 1-2 and PanIN 3 per mouse for the indicated mice (n=8-9 mice per group).

(G) The weight ratio of abdominal fat to body per mouse for KC and KC/Pd mice fed a high-fat diet (HFD) or control (Ctrl) as described in **Fig. 2B-E**.

(H) Ppard protein expression in pancreata in KC and KC/Pd mice fed HFD) or Ctrl as described in **panel G**, measured by Western blot. Ponceau S dye-stained bands in membrane were evaluated as an internal reference. "+" indicates the Ppard+ control.

(I) Representative images of H&E staining and co-immunofluorescence staining of CK19 and α -SMA or CK19 and amylase in pancreata of KC/Pd mice fed a GW diet (50 mg/kg) for 20 days.

(J) Representative images of H&E staining in pancreata of KC and KC/PdKO mice fed the GW (50 mg/kg) or control (Ctrl) diet for 13 weeks as described in **Fig. 3H-L**.

For **D** and **F**, the data are mean \pm SEM, * $P < .05$, and *** $P < .001$.

Figure S3

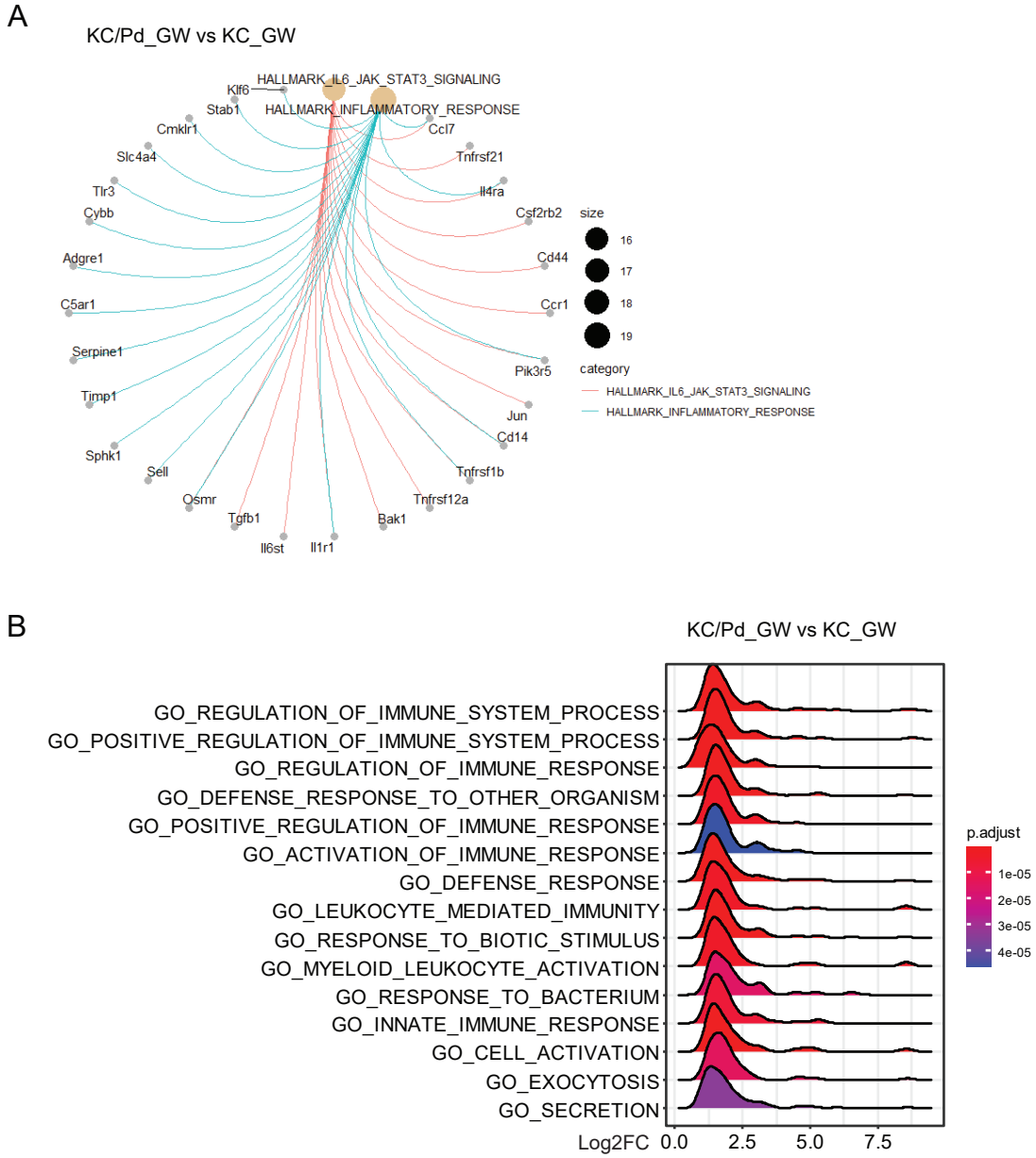
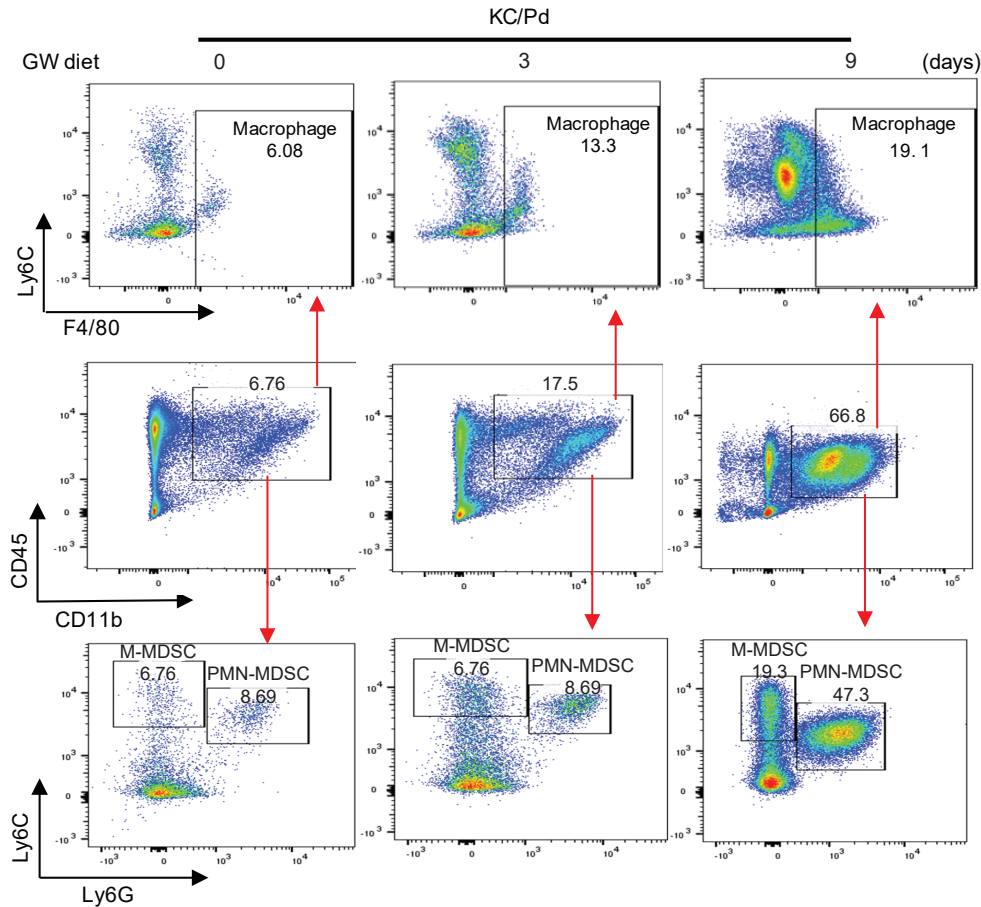


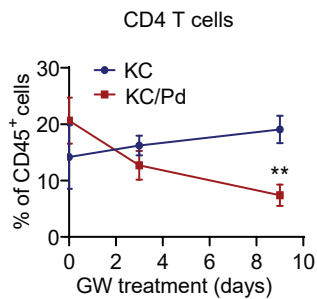
Figure S3. Ppard hyperactivation drives inflammatory response-related pathways identified by GSEA. Related to Figure 4.
(A) The Cnet plots of two top inflammatory response-related pathways using Hallmark gene sets, as described in **Fig. 4B**.
(B) GSEA results of KC and KC/Pd mice fed a GW diet for 3 days (KC_GW versus KC/Pd_GW), as described in **Fig. 4** using R package clusterProfiler, pAdj Cutoff=0.05, gene sets = MSigDB category “GO gene sets”. The ridgeline plots of top 15 enriched pathways.

Figure S4

A



B



C

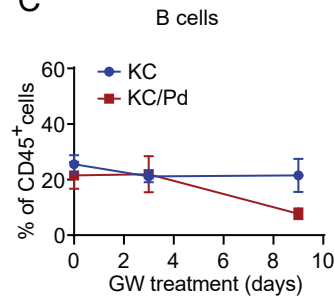


Figure S4. Ppard hyperactivation orchestrates an immunosuppressive microenvironment to promote pancreatic tumorigenesis in KC mice. Related to Figure 5.

(A-C) KC and KC/Pd mice at 6-8 weeks were fed the GW (50 mg/kg) for 0, 3, or 9 days ($n=3-5$ per group), and then euthanized. Their pancreata were examined for infiltrating immune cells assessed by flow cytometry as described in Fig. 5A-H. (A) Representative flow cytometry gating image results for pancreas-infiltrating macrophages ($CD45^+CD11b^+F4/80^+$), M-MDSCs ($CD45^+CD11b^+Ly6C^+Ly6G^-$) and PMN-MDSCs ($CD45^+CD11b^+Ly6C^+Ly6G^+$). (B, C) Percentage of $CD3^+CD4^+$ T cells (B) and B cells ($B220^+$) (C) among pancreas-infiltrating $CD45^+$ cells for the indicated mouse groups. Data are mean \pm SEM; ** $P < .01$.

Figure S5

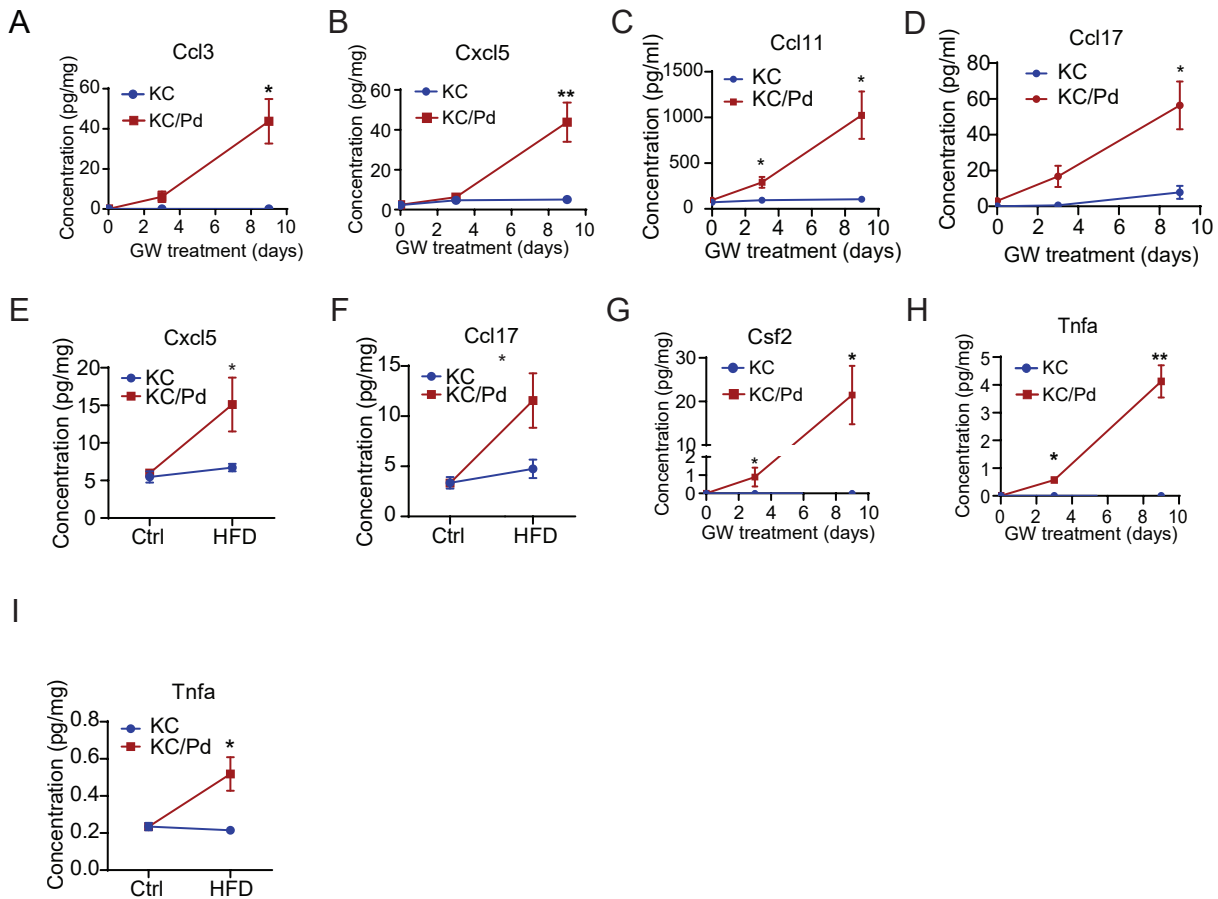


Figure S5. PPARD hyperactivation increases various chemokines and cytokines to establish an immunosuppressive microenvironment. Related to Figure 6.

(A-I) KC and KC/Pd mice at 6-8 weeks were fed the GW diet (50 mg/kg) for 0, 3, or 9 days, or a high-fat diet (HFD) or control (Ctrl) diet for 13 weeks, and then euthanized. The pancreata protein lysates were examined for a panel of chemokines and cytokines by Biolegend's LEGENDplex bead-based immunoassays as described in Fig. 6A-L (n=3-5 per group). (A-F) Chemokine protein concentration of pancreata from KC or KC/Pd mice fed the GW diet for Cxcl5 (A), Cxcl5 (B), Ccl11 (C), and Ccl17 (D), or fed either the HFD or Ctrl diet for Cxcl5 (E), and Ccl17 (F) are shown. Cytokine protein concentrations of pancreata from KC or KC/Pd mice fed the GW diet for Csf2 (G) and Tnfa (H) or fed either the HFD or Ctrl diet for Tnfa (I) are shown. Data are mean \pm SEM; * $P < .05$, ** $P < .01$.