

SUPPLEMENTARY FIGURE LEGENDS

Figure S1. A, Gene set enrichment analysis (GSEA) of RNA-seq data performed on tdTomato(+) acinar cells exposed to caerulein and 3 weeks of recovery versus tdTomato(+) acinar cells exposed to caerulein and 2 days of recovery. Top up- and down-regulated pathways are shown. **B,** PCA plot generated of the ATAC-seq data collected from tdTomato(+) acinar cells exposed to either saline or caerulein and allowed to recover for either 2 days or 3 weeks. Each point represents data obtained from a biological replicate mouse. **C,** Heatmap of ChromVar results characterizing the enrichment of known and *de novo* sequence transcription factor motifs in respective conditions. The top 75 motifs are shown. **D,** Venn diagram of motifs upregulated (green) and downregulated (red) in the corresponding contrasts.

Figure S2. A, Immunofluorescence for Sox9, TdTomato and DAPI staining of pancreas sections collected 2 days and 12 weeks after caerulein-induced pancreatitis. Representative images shown are from a total of N=2-5 mice per condition. **B,** Immunofluorescence for Cpa1, CK19 and DAPI staining of pancreas sections collected 2 days and 12 weeks after caerulein-induced pancreatitis. Representative images shown are from a total of N=2-5 mice per condition. **C,** UMAP projection of single-cell RNA-seq data generated with cells isolated from pancreata collected 2 days and 6 weeks after saline or caerulein treatment. **D,** Feature plots generated using single-cell RNA-seq data (subset on the epithelial compartment) for the indicated acinar/ductal/progenitor transcripts. **E,** Heatmap of single cell RNA-seq data on the epithelial compartment; Top 50 differentially expressed genes identified by comparing ductal versus acinar cell clusters ($\log_2FC > 1$), wherein each column represents a single cell. **F,** Heatmap of all differentially expressed genes identified by comparing caerulein + 2d recovery and saline + 2d recovery ($p_{adj} < 0.01$). **G,** Representative chromatin accessibility tracks at PanIN/duct/acinar genes visualized with IGV; light-blue boxes highlight chromatin dynamics that are up at 2 days and 3 weeks of recovery and lost with prolonged recovery; green boxes denote persistently accessible regions; dark-blue boxes represent regions that are lost and then regained with prolonged recovery. Scale bar for all tracks 0-60.

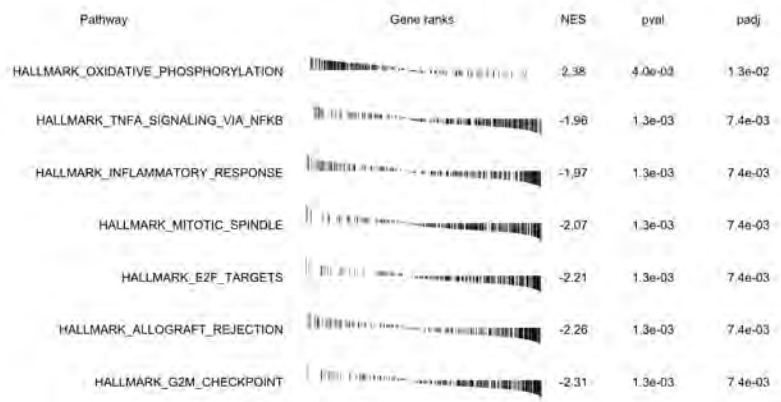
Figure S3. A & C, Schematic representations of primary pancreatitis and inflammatory re-challenge treatment regimen in wild-type mice. **B & D,** Hematoxylin and eosin staining of inflammation-naïve and inflammation-resolved mouse pancreas sections collected 2 days after inflammatory re-challenge. Representative images from a total of N=3-5 mice per condition (B) or images from all mice (D) are shown.

Figure S4. A, Schematic representation of lineage-traced mouse model exposed to primary treatment (saline or caerulein), 3 weeks of recovery, and then 3 weeks of mutant Kras activation. **B,** H&E and Alcian blue staining of mouse pancreas sections collected from mice previously exposed to either saline or caerulein plus 3 weeks of recovery, then 3 weeks of Kras^{G12D}. Representative images shown are from a total of N=2-5 mice per condition. **C,** H&E staining of inflammation-naïve and inflammation-resolved lineage-traced mice, after 12 weeks of recovery and then 2 days of Kras^{G12D}. **D & E,** Immunofluorescence for (D) Cpa1 and CK19 and (E) Dclk1 and DAPI staining of pancreas sections collected from inflammation-naïve and inflammation-resolved mice after 12 weeks of recovery and then 2 days of mutant Kras. **F,** GSEA of RNA-seq data comparing inflammation-naïve and inflammation-resolved tdTomato(+) acinar cells after 12 weeks of recovery and then 2 days of Kras^{G12D}. **G,** Representative chromatin accessibility tracks at PanIN-specific genes visualized with IGV; light green boxes highlight persistently accessible regions.

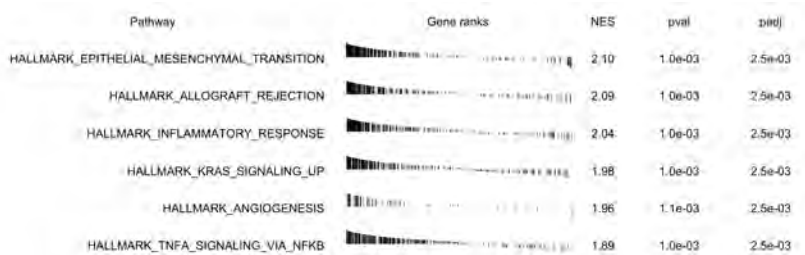
Figure S1

A

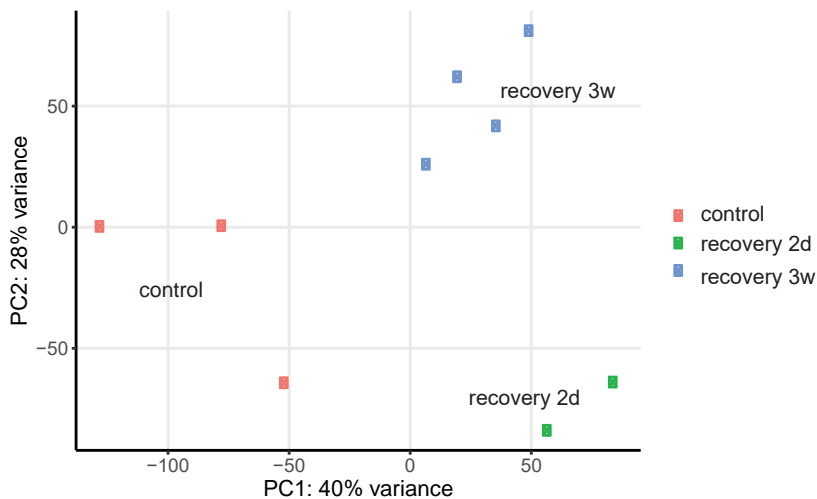
recovery 3 wks versus recovery 2 days



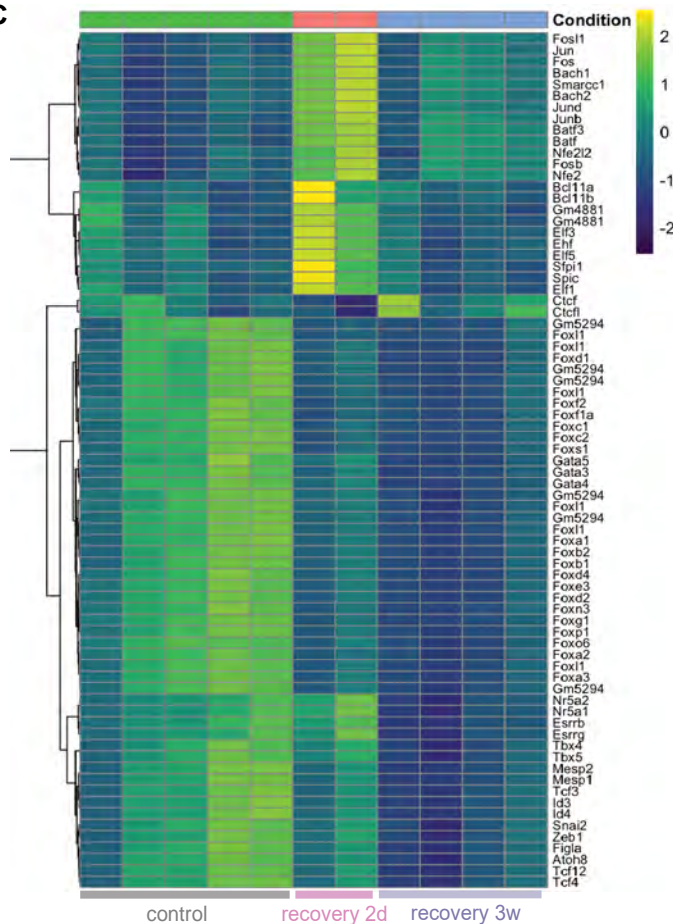
recovery 2 days versus control



B



C



D

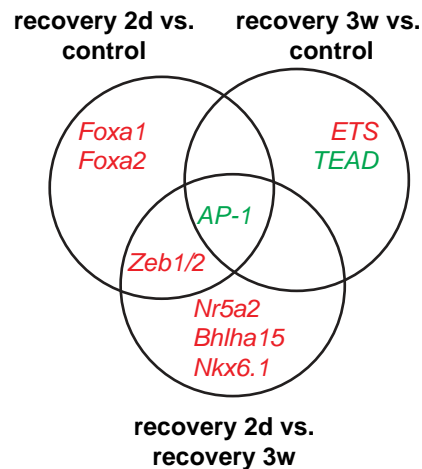


Figure S3

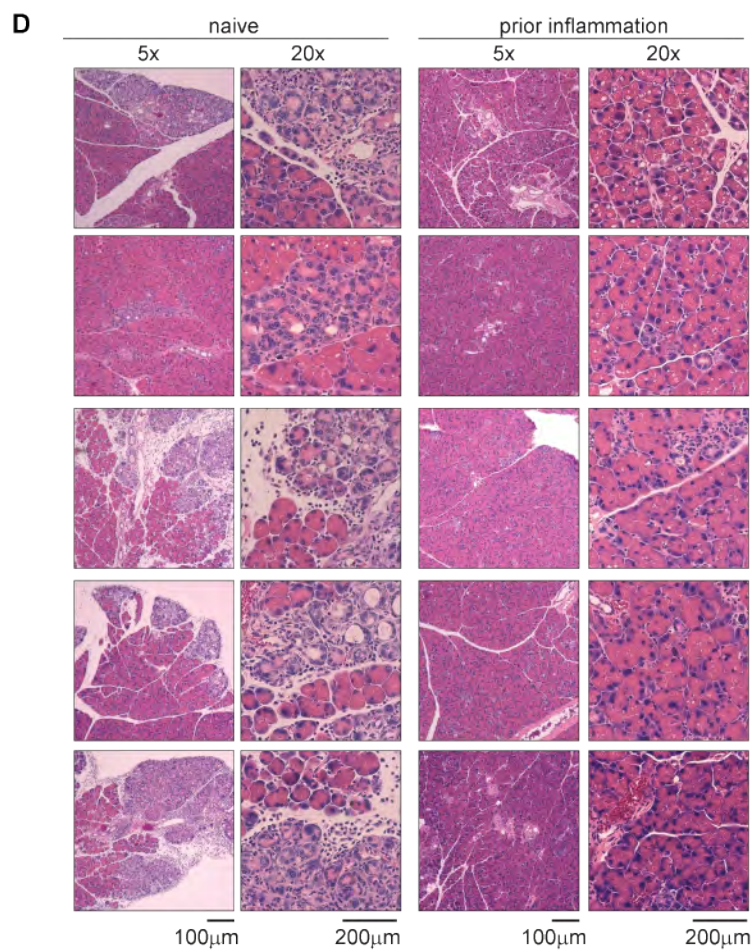
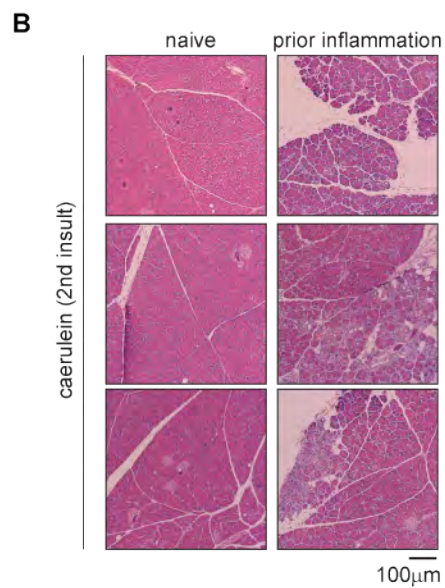
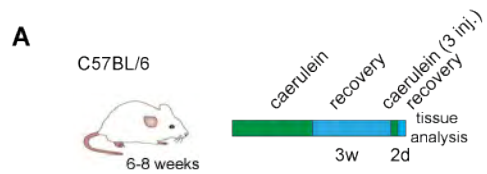


Figure S4

