Supplemental Figure Legends

Figure S1. IL6 is up-regulated in pancreatic cancer and required for PanIN formation

(**A**) Immunohistochemistry for IL6 in human pancreatic cancer. Red arrows indicate epithelial cells and green arrows indicate stromal cells. Scale bar 50μm. (**B**) Co-immunofluorescence staining for IL6 (green), SMA or CD45 (red), CK19 (magenta) and DAPI (blue). Scale bar 50μm. (**C**) IL6 immunostaining of primary mouse pancreatic fibroblasts exposed to conditioned medium from mouse pancreatic cancer cells. Scale bar 50μm. (**D**) RT-qPCR for *Il6* expression in primary mouse pancreatic fibroblasts exposed to conditioned medium from mouse pancreatic cancer cells. Data represent mean ± SEM, n=3. (**E**) Il6 expression in primary and commercial human pancreatic cancer cells. (**F**) Experimental design. (**G**) RT-qPCR for *Kras** and *Il6* expression in WT, iKras* and iKras*;IL6$^{-/-}$ mice pancreata. (**H**) Pathological analysis. Data represent mean ± SEM, n=3. The statistical difference was determined by two-sided Student's t-test. **p<0.01, ***p<0.001, $^{\#}$not significant. **(I)** HE and immunohistochemistry staining for IL6, p-Stat3 and p-ERK1/2 in iKras*, iKras*;IL6$^{+/-}$ and iKras*;IL6$^{-/-}$ mice pancreata. Scale bar 50μm.

Figure S2. Characterization of pancreatic immune infiltrate in iKras*;IL6$^{-/-}$ mice

(**A**) Pancreatic immune cell infiltrate was measured by flow cytometry to determine the percentage of CD45^{+} immune cells, CD3^{+} T cells, CD3^{+}/CD8^{+} Tc cells, CD3^{+}/CD4^{+} Th cells, CD3^{+}/CD4^{+}/CD25^{+}/FoxP3^{+} Treg cells, CD11b^{+}/F4/80^{+} macrophages, CD11b^{+}/Gr-1^{+} MDSCs, CD11b^{+}/Gr-1^{low} MO-MDSCs and CD11b^{+}/Gr-1^{hi} PMN-MDSCs. (**B**) Toluidine blue staining for mast cells in iKras* and iKras*;IL6$^{-/-}$ mice pancreata. Scale bar 25μm.

Figure S3. IHC staining of IL6, p-Stat3, p-Akt and SMA in iKras* and iKras*;IL6$^{-/-}$ pancreata

(**A**) IL6; (**B**) p-Stat3; (**C**) p-Akt and (**D**) SMA levels in iKras* and iKras*;IL6$^{-/-}$ pancreata measured by immunohistochemistry. Scale bar 25μm.

Figure S4. IL6 regulates the fibro-inflammatory environment and survival of pancreatic cancer

(**A**) RT-qPCR for *MMP7*, *MMP9*, *MT1MMP* and *TIMP1* genes. Data represent mean ± SEM, each point indicates one animal. *p<0.05. (**B**) RT-qPCR for *Il2*, *Il4*, *Il10*, *Il11*, *Il17*, *Cox2*, *Tnfα* and *Ifnγ*. Data represent mean ± SEM, each point indicates one animal. (**C**) TUNEL staining in iKras* and iKras*;IL6$^{-/-}$ pancreata. Scale bar 25μm.

Figure S5. IL6 regulates ROS accumulation and survival of PanIN cells

(**A**) Cleaved caspase 3 measured by immunohistochemistry in iKras* and iKras*;IL6$^{-/-}$ pancreata. Scale bar 25μm. (**B**) RT-qPCR for pro-/anti-apoptotic genes ratio. Data represent mean ± SEM, each point indicates one animal. *p<0.05, **p<0.01. (**C**) Bright field images of primary mouse pancreatic cancer cell line 9805 treated with 600 μM H_2O_2 alone, or in the presence of IL6 (50 ng/ml), or IL6 pre-incubated with anti-IL6 (8 μg/ml), for 1h. Scale bar 50μm. (**D**) Experimental design: NAC treatment was started in iKras*;IL6$^{-/-}$ mice two weeks after pancreatitis induction and sustained for three weeks. (**E**) HE and and immunohistochemistry staining for p-ERK1/2, p-Stat3 and Ki67 in NAC treated iKras*;IL6$^{-/-}$ mice. Scale bar 50μm.

Figure S6. MAPK and IL6 signaling pathways activity following Kras* inactivation

(**A**) Experimental design. (**B**) RT-qPCR for mutant *Kras** and *Il6* genes in control, iKras* and iKras*;IL6$^{-/-}$ pancreata. Data represent mean ± SEM, each point indicates one animal. (**C**) Western blot for p-ERK1/2, total-ERK1/2, p-Stat3, p-Akt, total-Akt, Cleaved caspase 3 and GAPDH in iKras* and iKras*;IL6$^{-/-}$ pancreata. (**D**) IL6 and (**E**) p-Stat3 measured by immunohistochemistry in iKras* and iKras*;IL6$^{-/-}$ pancreata. Scale bar 25μm.

Figure S7. IL6 deficiency facilitates tissue repair following Kras* inactivation

(**A**) PAS; (**B**) SMA immunohistochemistry and (**C**) Trichrome staining in iKras* and iKras*;IL6$^{-/-}$ pancreata. Scale bar 50μm.

Figure S8. Acinar cell proliferation contributes to faster recovery following Kras* inactivation in IL6 deficient mice

(**A**) Mist1 immunohistochemistry. Scale bar 25μm. (**B**) Ki67 immunohistochemistry. Scale bar 25μm. (**C**) Co-immunofluorescence staining for CK19 (red), Ki67 (green), SMA (magenta) and DAPI (blue). Scale bar 25μm. (**D**) Ki67 proliferation index in CK19(+), CK19(-) epithelium and SMA(+) stroma. Data represent mean ± SEM, n=3. The statistical difference was determined by two-sided Student's t-test. *p<0.05, **p<0.01.