**Supplementary Figure 1. Deletion of USP22 in tumor cells increases T cell infiltration and decreases myeloid cell infiltration.** (A) Boxplot of *Usp22* gene expression (transcripts per million (tpm)) in YFP+ tumor cells sorted from subcutaneously implanted T-cell-low and T-cell-high tumors (n=8 different PDA tumor cell clones/group). (B) Immunofluorescent staining of subcutaneously implanted T-cell-low and T-cell-high tumors in vivo for USP22 (red). (C) Quantitative PCR analysis for Usp22 in CRISPR-mediated Usp22 knockout PDA tumor cell clones (6 knockout 6419c5 tumor cell clones). (D) Flow cytometric analysis of subcutaneously implanted 6419c5 *Usp22*-WT and *Usp22*-KO tumors (6 independent knockout clones, n=4-27 tumors/group). (E) Tumor weights of implanted *Usp22*-WT and *Usp22*-KO tumors (2 independent KO clones, n=4-7/group). (F) Flow analysis of EdU incorporation in *Usp22*-WT and *Usp22*-KO tumor cells cultured *in vitro* (n=3-8/group) (G-H) Growth curves (G) and final tumor weights (H) of 6419c5 *Usp22*-WT and *Usp22*-KO tumors with or without T cell depletion (n=5 mice/group). (I) Quantitative PCR analysis for *Usp22* in CRISPR-mediated *Usp22* knockout PDA tumor cell clones (2 knockout 6422c1 tumor cell clones). (J) Flow cytometric analysis of subcutaneously implanted 6422c1 *Usp22*-WT and *Usp22*-KO tumors (2 knockout clones, n=4-12 tumors/group). (K) Quantitative PCR analysis for *Usp22* in CRISPR-mediated Usp22 knockout PDA tumor cell clones (2 knockout 6694c2 tumor cell clones). (L) Flow cytometric analysis of subcutaneously implanted 6422c1 Usp22-WT and Usp22-KO tumors (2 independent knockout clones, n=4-8 tumors/group). In (A, D-F, H, J, & L), data are presented as boxplots with horizontal lines and error bars indicating mean and range, respectively. Statistical differences between groups were calculated using Student’s unpaired t-test. In (C, I, and K), data are presented as bar graphs with error bars indicating standard error of mean. Statistical differences between groups were calculated using one-way ANOVA with multiple comparison. \* indicates p<0.05, \*\* p<0.01, and \*\*\* p< 0.001. Scale bars, 200 m.

**Supplementary Figure 2. USP22 loss promotes anti-tumor immunity in orthotopic PDA tumors and suppresses lung metastasis.** (A) Flow cytometric analysis of orthotopically implanted *Usp22*-WT and *Usp22*-KO tumors (2 independent knockout clones, n=4-9 tumors/group). (B-C) Flow cytometric analysis of lungs following tail veil injection of *Usp22*-WT and *Usp22*-KO tumor cells (2 independent KO clones, n=5-10 mice/group). (D) Quantification of lung weight 14 days after tail vein injection of 6694c2 Usp22-WT and Usp22-KO tumor cells (2 independent knockout clones) (n = 5 mice/group). (E) Flow cytometric analysis of lungs following tail veil injection of 6694c2 *Usp22*-WT and *Usp22*-KO tumor cells (2 independent KO clones, n=5-10 mice/group). In (A-E), data are presented as boxplots with horizontal lines and error bars indicating mean and range, respectively. In (A & C-E), statistical differences between groups were calculated using Student’s unpaired t-test. In (B), statistical differences between groups were calculated using two-way ANOVA analysis with multiple comparison test. \* indicates p<0.05, \*\* p<0.01, and \*\*\* p< 0.001.

**Supplementary Figure 3. Knockdown of ATXN7L3 in tumor cells increases T cell infiltration and decreases myeloid cell infiltration.** (A) Representative images of 3 T-cell-low PDA tumor cell clones in culture stained for USP22 (red) and YFP (green). All images in (A) are at 20X magnification. (B) Quantitative PCR analysis for *Atxn7l3* following shRNA-mediated knockdown in clone 6419c5 (2 knockdown tumor cell lines examined). (C) Flow cytometric analysis of tumor-infiltrating immune cells in implanted 6419c5-EV and 6419c5-Atxn7l3-knockdown tumors (2 independent knockdown cell lines, n=4-8 tumors/group). (D) Quantitative PCR analysis for *Atxn7l3* following shRNA-mediated knockdown in clone 6694c2 (2 knockdown tumor cell lines examined). (E) Flow cytometric analysis of tumor-infiltrating immune cells in implanted 6694c2-EV and 6694c2-Atxn7l3-knockdown tumors (2 independent knockdown cell lines, n=4-8 tumors/group). In (B and D), data are presented as bar graphs with error bars indicating standard error of mean. In (C & E), data are presented as boxplots with horizontal lines and error bars indicating mean and range, respectively. In (B and D), statistical difference between groups were calculated using one-way ANOVA with multiple comparison. In (C & E), statistical differences between groups were calculated using Student’s unpaired t-test. \* indicates p<0.05, \*\* p<0.01, and \*\*\* p< 0.001.

**Supplementary Figure 4. USP22 loss leads to transcriptional reprogramming of tumor cells.** (A) Dendrogram showing unsupervised clustering of RNA-seq samples using top 2000 most variably expressed genes across 9 samples (3 Usp22-WT samples, 3 Usp22-KO(A) samples, and 3 Usp22-KO(B) samples) using hclust method. (B) Leading-edge plot from the GSEA analysis showing two Usp22-KO tumor cell-enriched genesets: Hallmark\_Interferon\_alpha\_response and Hallmark\_Interferon\_gamma\_response genesets. (C) Leading-edge plot from the GSEA analysis showing one Usp22-WT tumor cell-enriched geneset: Hallmark\_E2F\_targets. (D) Transcript per million (TPM) of a group of interferon response genes as well as regulatory factors for myeloid cell and regulatory T cells based on the RNA-seq results. (E) Flow analysis of surface PD-L1 and MHCI on tumor cells with and without treatment of 24hr IFN-γ. (F) Bar graphs showing predicted transcriptional regulators for Usp22-KO tumor cells (left, red) or Usp22-WT tumor cells (right, blue). Differentially expressed genes (padj value < 0.01 and absolute fold change >2) were used as input for EnrichR analysis (ChEA dataset). In (D), statistical differences between groups were calculated using DESeq2 analysis. In (E), statistical differences between groups were calculated using one-way ANOVA with multiple comparison.