

HMGA2 Expression in Pancreatic Ductal Adenocarcinoma Controls Tumor Microenvironment and Immunosuppression via IL1 α

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PDAC Treatment Lags in Precision Medicine Efforts

- Pancreatic ductal adenocarcinoma (PDAC) incidence rates are rising in the US.
- No clinically validated biomarkers exist to aid clinicians in determining the best treatment strategies.
- Basal subtype PDAC is associated with worse outcomes, an immunosuppressive tumor microenvironment (TME) and potentially better response to inhibitors of RAS.
- We have previously shown that the chromatin architectural factor high mobility group A2 (HMGA2) can be detected by IHC, defines the basal subtype, and is associated with more FAP+ fibroblasts and fewer CD8+ T cells.

HMGA2 Alters Fibroblast Phenotype

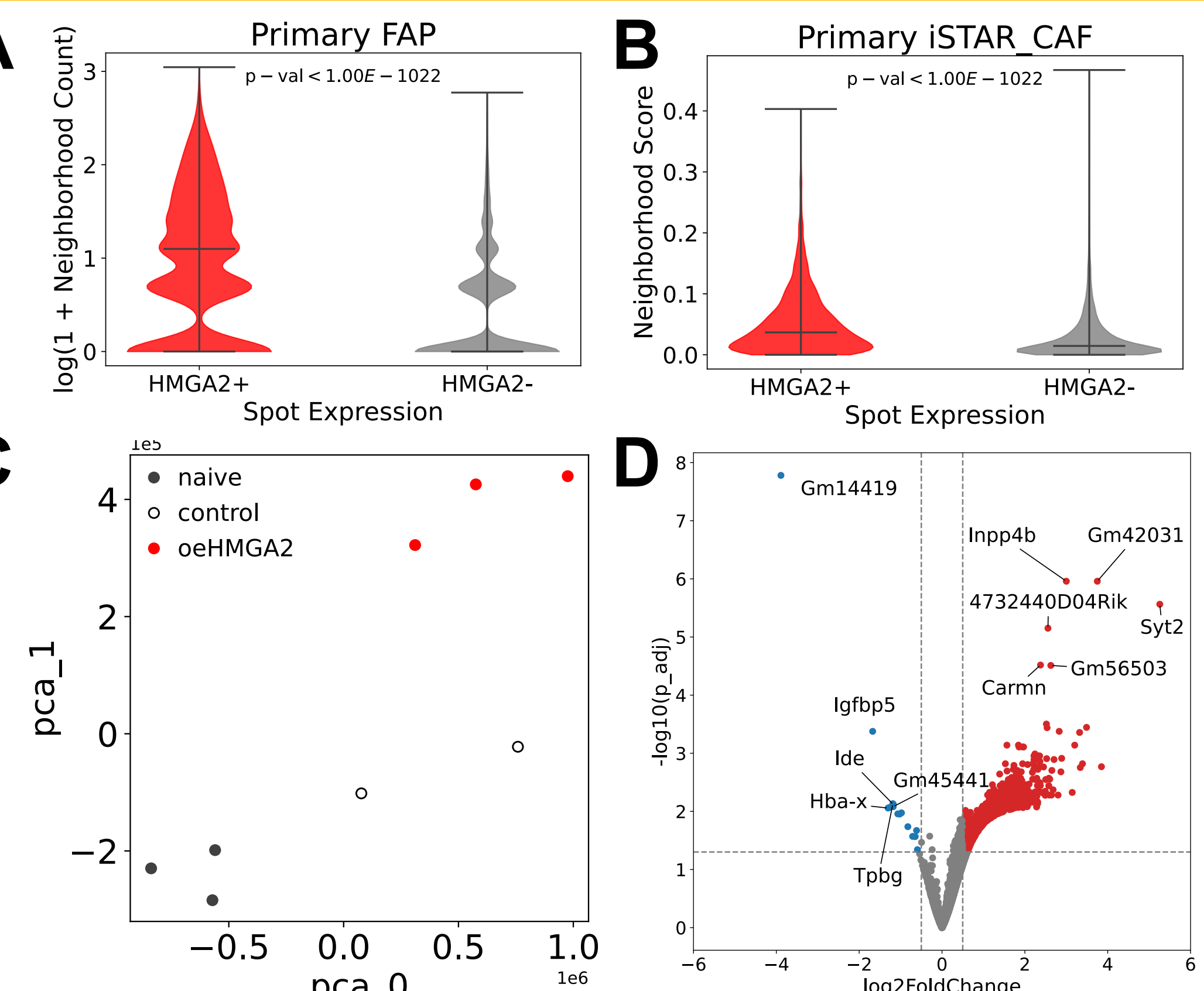


Figure 1. A-B) Expression of HMGA2 in primary tumors predicts increased FAP+(A) expression and cancer-associated fibroblast (CAF) (B) signatures in the immediate neighborhood in spatial transcriptomics data (Pei et al, 2025). **C)** Media from KPCY cell lines overexpressing HMGA2 conditions pancreatic fibroblasts farther away from naïve populations than control media. **D)** Volcano plot of differentially expressed genes in media-treated pancreatic fibroblasts. oeHMGA2 media-treated fibroblasts downregulated GSEA pathways associated with NK cell response and chemokine binding.

HMGA2 Controls Transcription of IL1A and Increases LRRC15+ IL6+ α SMA+ CAFs

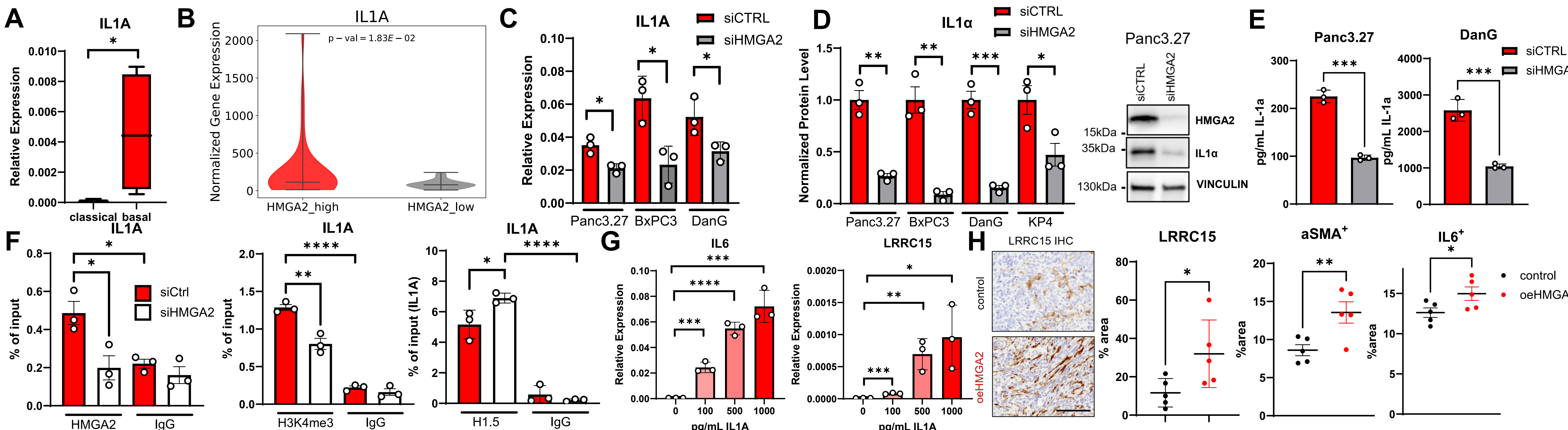


Figure 2. A) qPCR of HMGA2^{high} basal lines versus HMGA2^{low} classical lines shows differences in expression of IL1A. **B)** RNAseq of 79 patient samples shows that HMGA2+ tumors have higher IL1A expression. **C)** siRNA-mediated knockdown of HMGA2 leads to loss of IL1A expression in basal cell lines. **D)** Quantification of Western blot of whole cell lysates shows decreased IL1 α with knockdown of HMGA2. Representative blot on right. **E)** Quantification of IL1 α in cell culture supernatant shows decreased levels with HMGA2 knockdown. **F)** Chromatin immunoprecipitation in Panc3.27 cells shows HMGA2 at the IL1A promoter associated with increased H3K4me3 and displacement of linker histone H1.5. **G)** Naïve pancreatic fibroblasts treated with IL1 α increase transcription of IL6 and LRRC15. **H)** KPCY cell lines with HMGA2 overexpression induce higher LRRC15, α SMA, and IL6 levels in CAFs compared to controls.

HMGA2/IL1 α Axis Drives Immunosuppression

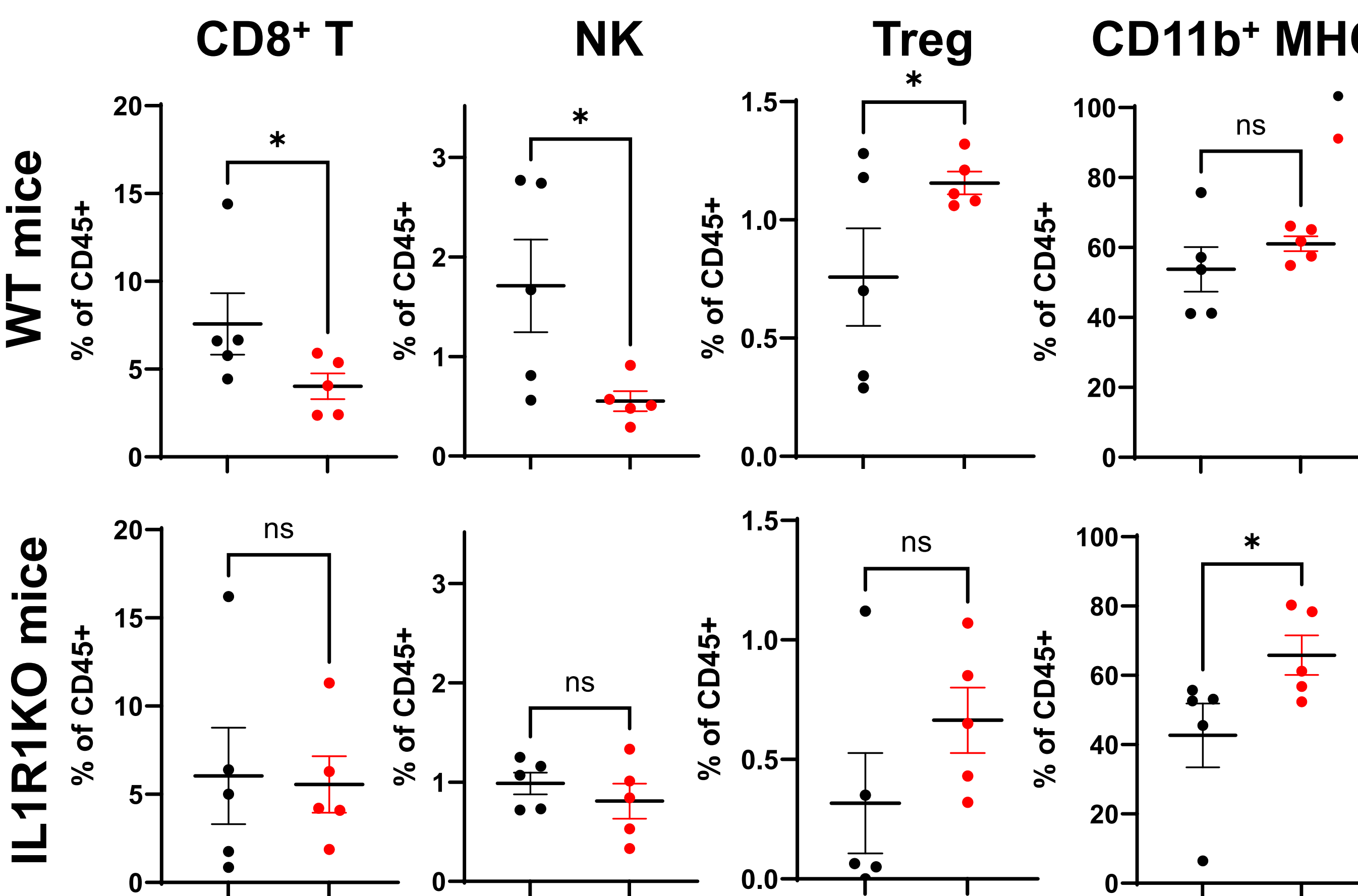


Figure 3. 2838c3 KPCY cell line engineered to overexpress HMGA2 injected into the pancreas syngeneic wild-type (top) or IL1R1KO (bottom) mice, grown for 21 days, and harvested for multiparameter flow cytometry. In wild-type recipients, intratumoral CD8+ T cells and NK cells decrease in oeHMGA2 tumors, while Tregs increase. IL1R1KO recipients have no significant difference in CD8+ T cells, NK cells, or Tregs between control and oeHMGA2 tumors, but CD11b+ MHCII- cells increase with oeHMGA2. Lung metastases were increased in oeHMGA2 tumor-bearing WT mice but not IL1R1KO mice. Primary tumor volumes were larger in oeHMGA2 conditions in both genotypes.

RASi + α IL1RAP (Nadunolimab) Reverses Immunosuppression

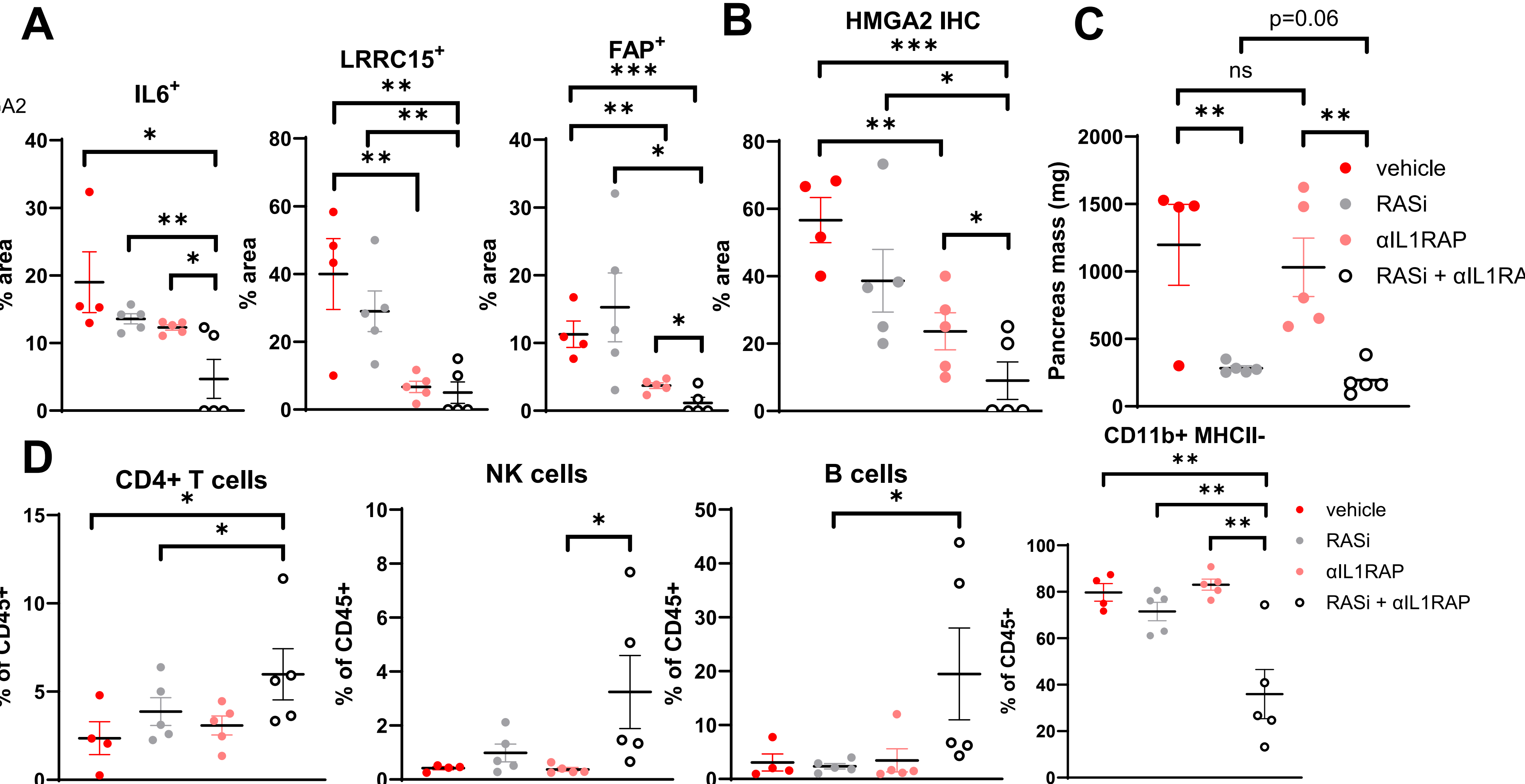


Figure 4. A) Fibroblast polarization is altered by α IL1RAP and RASi treatment of HMGA2+ KPCY cell line. **B)** HMGA2+ tumor burden was most decreased in combination arm. **C)** Pancreas mass significantly decreased with RASi and α IL1RAP. **D)** Large pro-immune population alterations are seen in combination treated tumors.

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