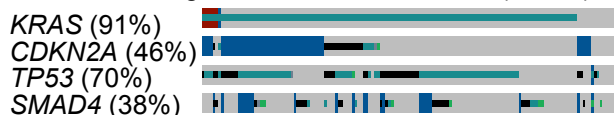
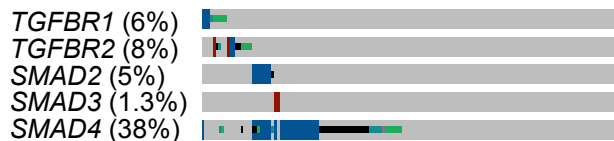


## Supplementary Fig. S1

### A Most common genetic alterations in PDA (TCGA):



### TGF- $\beta$ core pathway alterations in PDA (TCGA):



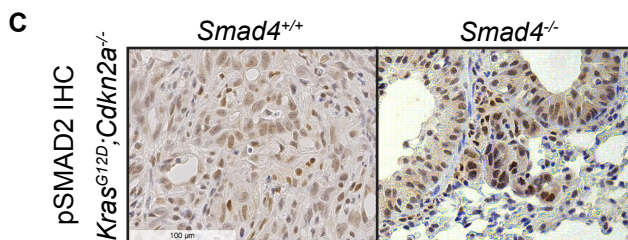
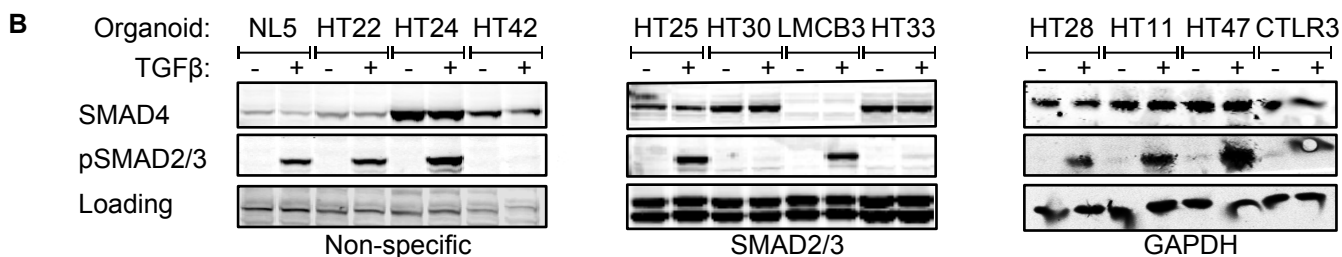
### Most common genetic alterations in PDA (UTSW):



### TGF- $\beta$ core pathway alterations in PDA (UTSW):

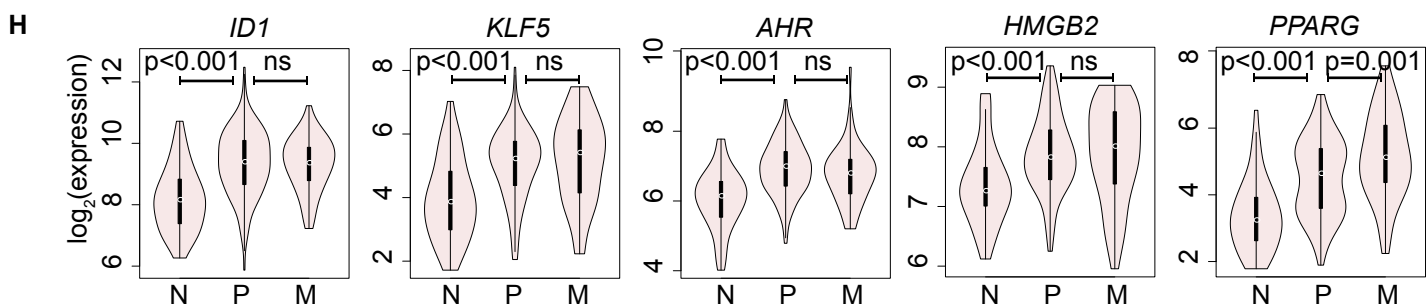
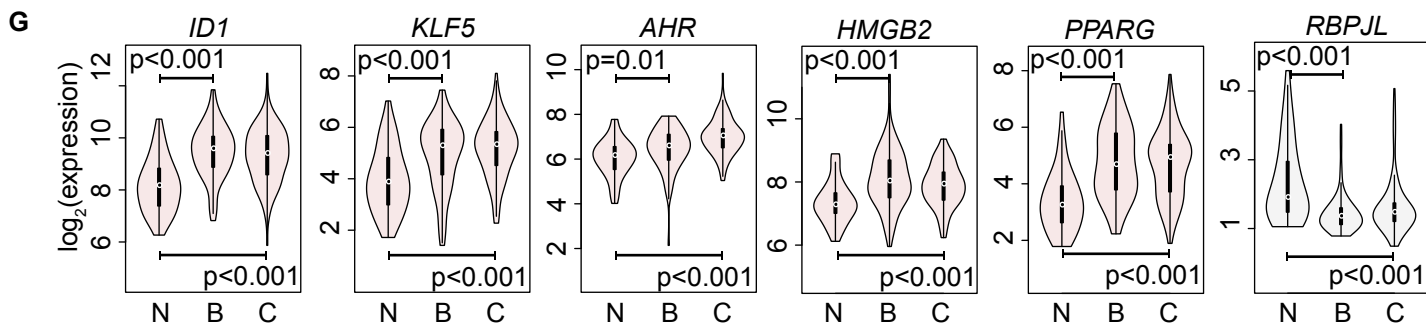
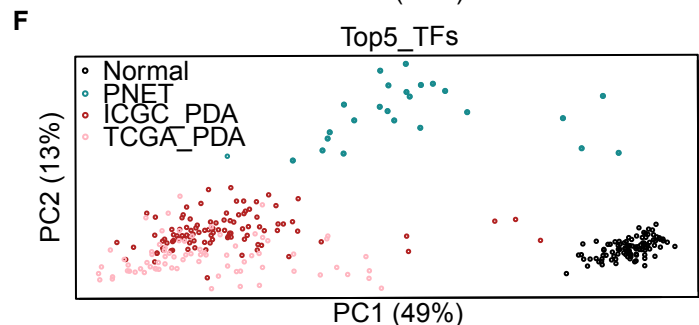
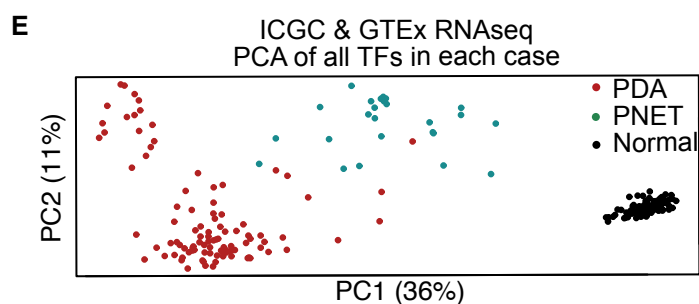


Genetic Alteration: ■ Amplification ■ Deep Deletion ■ Truncating Mutation ■ Missense Mutation (likely driver) ■ Missense Mutation (likely passenger)



### D

<i>AHR</i>	<i>FOS</i>	<i>JUND</i>	<i>NKX2-2</i>	<i>STAT1</i>
<i>ATF4</i>	<i>FOSB</i>	<i>KLF13</i>	<i>NKX6-3</i>	<i>STAT2</i>
<i>BCL6</i>	<i>HIF1A</i>	<i>KLF5</i>	<i>NPAS2</i>	<i>STAT3</i>
<i>BHLHA15</i>	<i>HMGA1</i>	<i>KLF6</i>	<i>NR4A1</i>	<i>STAT6</i>
<i>BHLHE40</i>	<i>HMGB1</i>	<i>MAFB</i>	<i>NR5A2</i>	<i>TFDP1</i>
<i>BPTF</i>	<i>HMGB2</i>	<i>MAZ</i>	<i>PAX6</i>	<i>TSC22D1</i>
<i>CREB3L1</i>	<i>HMGB3</i>	<i>MEF2A</i>	<i>PEG3</i>	<i>TSC22D3</i>
<i>DMTF1</i>	<i>HSF4</i>	<i>MEIS1</i>	<i>PPARG</i>	<i>TSHZ3</i>
<i>DRAP1</i>	<i>ID1</i>	<i>MEIS2</i>	<i>PRRX1</i>	<i>XBP1</i>
<i>EGR1</i>	<i>ID2</i>	<i>MLXIP</i>	<i>RBPJ</i>	<i>ZBTB16</i>
<i>EHF</i>	<i>ID3</i>	<i>MLXIPL</i>	<i>RBPJL</i>	<i>ZBTB38</i>
<i>ELF1</i>	<i>ISL1</i>	<i>MYC</i>	<i>RUNX1</i>	
<i>ELF3</i>	<i>JUN</i>	<i>NFE2L1</i>	<i>SREBF2</i>	
<i>EPAS1</i>	<i>JUNB</i>	<i>NFIC</i>	<i>ST18</i>	



### **Supplementary Fig. S1: TGF- $\beta$ signaling and transcriptional networks in PDA**

A) cBioportal oncoprints of common genetic alterations and TGF- $\beta$  pathway alterations in PDA. Each column represents one case.

B) Western immunoblot analysis of pSMAD2 and SMAD4 in human PDA organoids treated with or without 100 pM TGF- $\beta$  for 2h.

C) pSMAD2 immunohistochemistry (IHC) of mouse *Kras*<sup>G12D</sup>;*Cdkn2a*<sup>-/-</sup> PDA in the pancreas (*right*) and *Kras*<sup>G12D</sup>;*Cdkn2a*<sup>-/-</sup>;*Smad4*<sup>-/-</sup> PDA metastasis in the lung (*left*).

D) Genes represented within the top 5 expressed transcription factors of at least one sample in 225 samples of normal pancreas, PNET, and PDA.

E) PCA of GTEx and ICGC RNA-seq datasets from using the complete list of transcription factors expressed in these samples.

F) PCA of GTEx, ICGC, and TCGA RNA-seq datasets using the gene set in Supplementary Fig. S1D.

G) GEO2R analysis of the expression of the top PDA-enriched PC1 genes (refer to Figure 1E) in the pancreatic microarray dataset GSE71729. N=Normal pancreas, B=Basal PDA, C=Classical PDA. p-values are from two-sided, unpaired t-tests of B versus N, and C versus N.

H) GEO2R analysis of the expression of PDA-enriched PC1 genes in pancreatic microarray dataset GSE71729. N=Normal pancreas, P=Primary PDA tumor, M=Metastasis of PDA. P-values from two-sided, unpaired t-tests of P versus N, and M versus P.