

Figure S1| Curation of discovery and validation datasets of PDAC sc-RNA-Seq Data

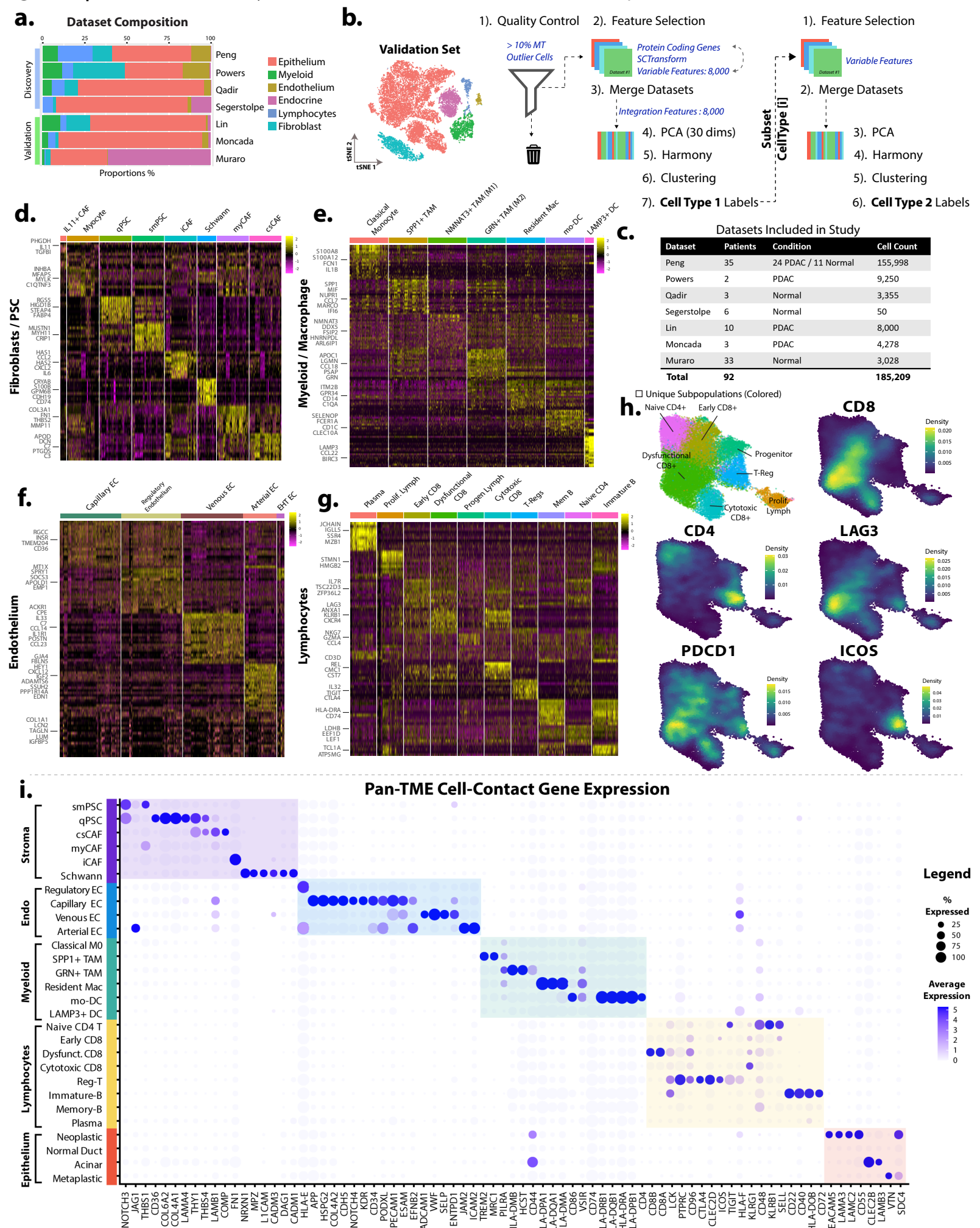


Figure S1 | Curation of validation set and secondary annotations a). Barplot shows the composition of major celltypes across the datasets included in the discovery and external validation set. Colored UMAP shows the cell type labels designated for each cell. **b).** Single cell data workflow outlines initial data quality controls, batch-effect removal, clustering, initial cell type annotation, and subsequent subpopulation clustering of integrated datasets. **c).** Table outlines the single cell datasets utilized in the study. **d-g).** Heatmap showing top differentially expressed (log fold change) marker genes of subpopulations within the fibroblast, myeloid, endothelial, and lymphocyte population. **h).** Further expression density plots that distinguish CD8, CD4, LAG3 (CD223), PD1 (PDCD1), and ICOS (CD278) among the lymphocytic subpopulation. (B-Lymphocytes removed for visualization). **i).** ECM and Cell-contact associated gene expression shown across the TME. (features were filtered by $FC > 0.8$). Source data are provided as a Source Data file.

Figure S2 | Stroma subtype associated changes across the tumor microenvironment

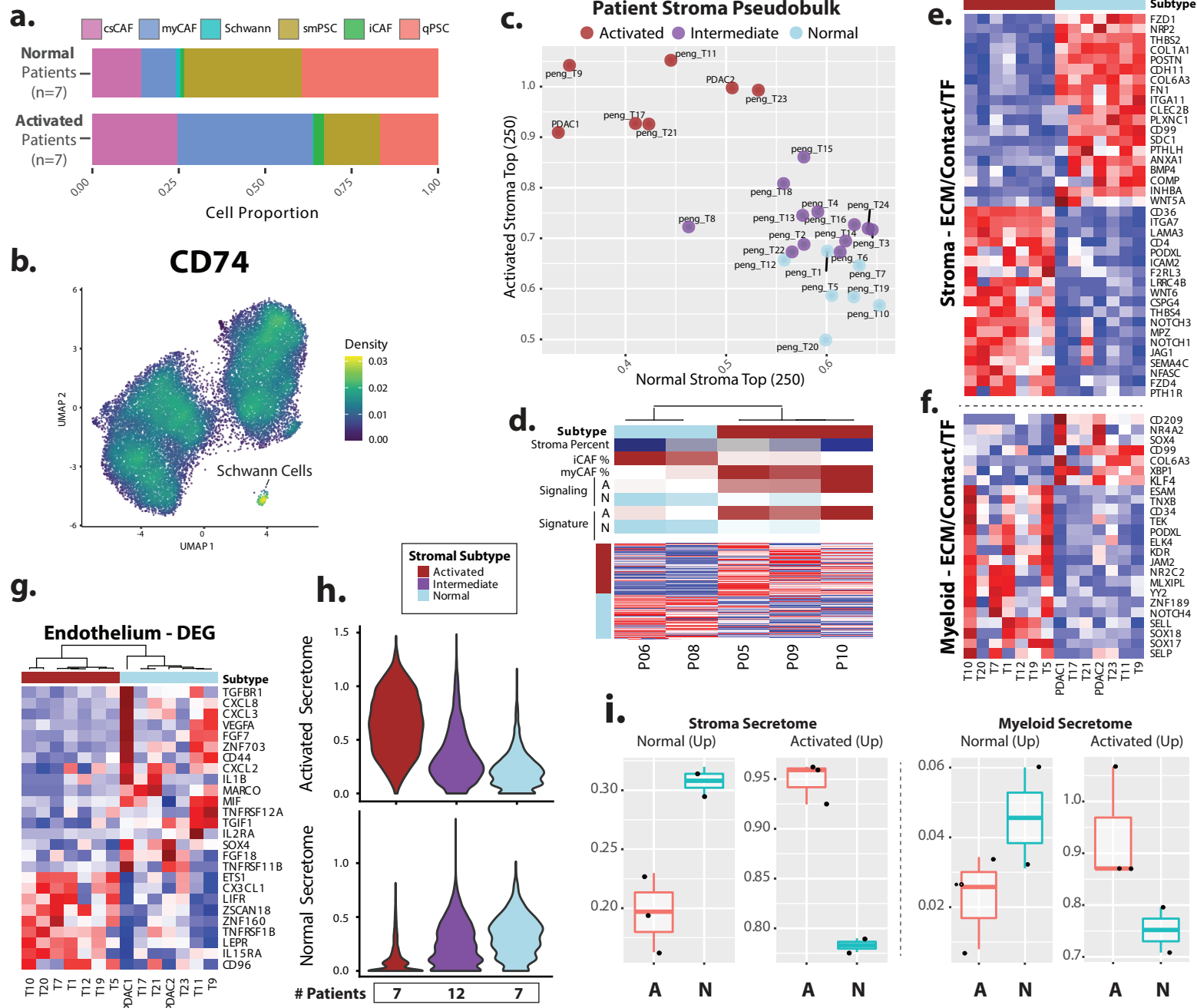


Figure S2 | Stromal subtype variations in discovery and validation set a). Segmented bar plot shows stromal cell subpopulation proportions comparison between the 7 most normal and 7 most activated patient samples. **b).** Density plot of CD74 expression in fibroblast/pericyte populations **c).** Stroma subtype signature scatterplot of discovery set samples shows purple intermediate patients which were excluded from secretome analysis. **d).** Heatmap shows subtype expression within the validation cohort. **e-f).** Heatmap showing differential ECM, cell-contact and transcription factors between the two subtypes for stroma and myeloid cells. **g).** Differential secretome heatmap of the endothelium between patient subtypes. **h).** The average expression of the top differential secretome candidates shown across subtype groups including intermediate patients. **i).** Boxplot represents the average expression of the discovery set-based secretome candidates by the validation set; A (activated) and N (normal); Validation patient stroma (left) and myeloid compartment (right). Source data are provided as a Source Data file.

Figure S3 | Tumor subtype signatures highlights potential autocrine signaling targets

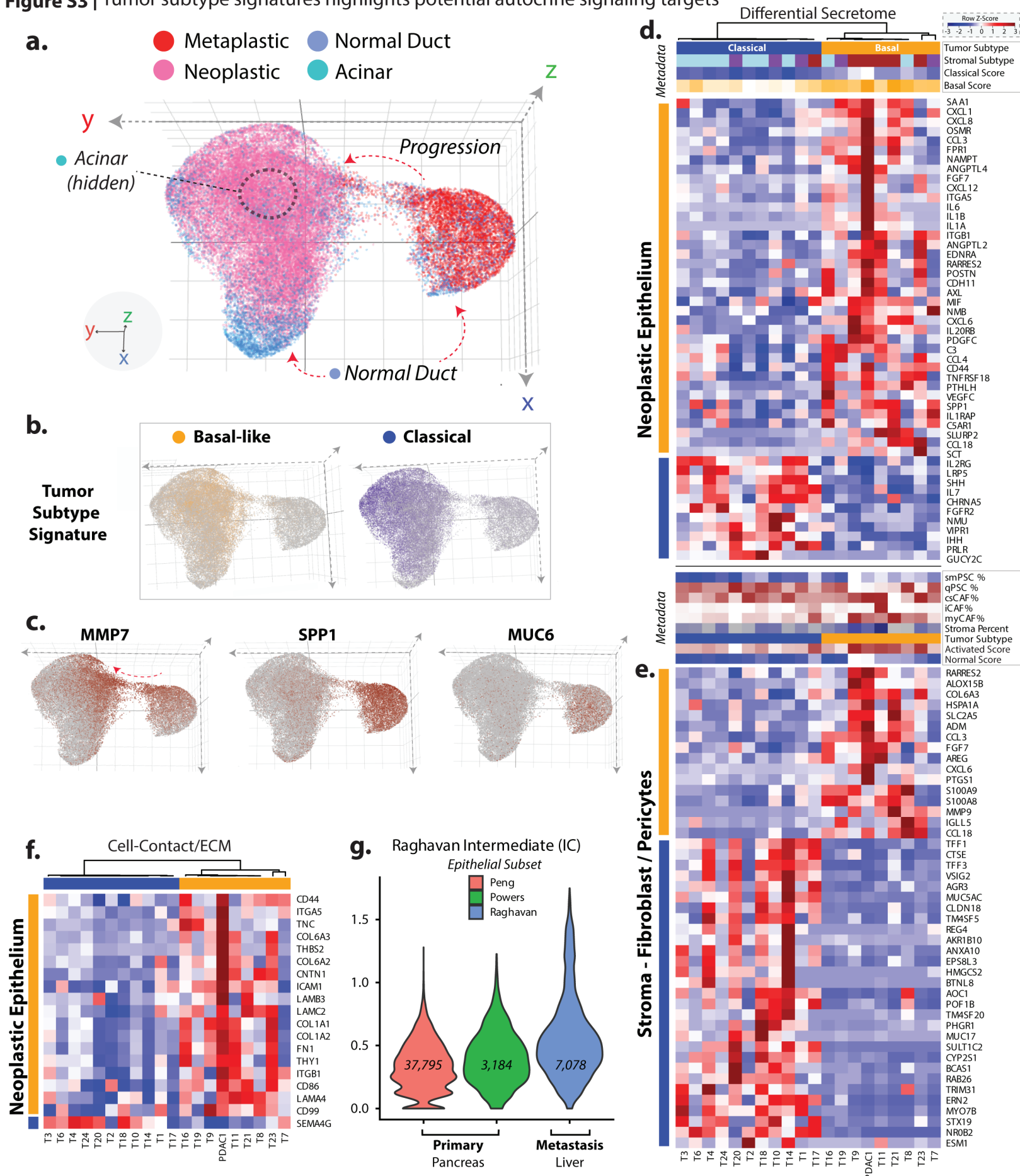


Figure S3 | Tumor subtype dependent autocrine signaling a). 3D UMAP projection of the PDAC derived epithelia with an alternate perspective highlighting potential relationships between cells. **b).** Tumor subtype signature scores (basal and classical) are enriched in spatially distinct zones. **c).** Inflammation and tumorigenesis markers are localized to the metaplastic cell cluster. MMP7 expression demonstrates a bridge between metaplasia and neoplasia (red arrow). **d).** Gene expression heatmap shows the differential autocrine signaling between the basal-like and classical cancer cells for each patient. **e).** Differential expression of patient stroma (fibroblast/pericytes) based on basal/classical subtypes. Column tracks show correlated metadata. **f).** Heatmap showing cell-contact related genes between the tumor subtypes. **g).** Violin plot shows relative signature score for intermediate (IC) between primary and metastasis derived single cell data. Source data are provided as a Source Data file.

Figure S4 | Distinct TME profiles emerge based on cross compartment phenotypes

a.

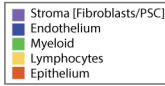


Cross Compartment Correlation Matrix

Cell Type - Specific
Gene Signature
Scores

b.

Derived Cell Type



* p -value < 0.05

C.

Derived Cell Type

- Stroma
- Endothelium
- Myeloid
- Lymphocytes
- Epithelium

Feature Group

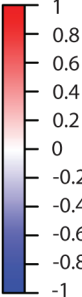
- Interleukins
- TGFB
- IFNG
- Subtypes
- Metabolism
- Drug Response

Length



Significance

* $p < 0.05$



IL17-Signaling	Green
NFkB-Signaling	Green
Hypoxia	Green
IL10-Antinflammatory	Green
TGFb-Signaling	Green
IL17-Signaling	Green
Mesenchymal	Green
Toll-like Receptor	Green
Macrophage (M0)	Green
Notta Basal A	Green
TSLP Signaling	Green
Moffitt Activated [25]	Green
IL1-Signaling	Green
TGFb Production	Green
TGFb Production	Green
TGFb Response	Green
Complement Pathway	Green
Classical Pathway	Green
Matrix Metalloproteinase	Green
TNF-Signaling	Green
IL3-Signaling	Green
Moffitt Basal [25]	Green
NFkB-Signaling	Green
Alternatively Activated	Green
PI3K/Akt Pathway	Green
Glycolytic Pathway	Green
PPAR Pathway	Green
Epi EMT	Green
TGFb Response	Green
Tuveson iCAF	Green
Tuveson myCAF	Green
Endo EMT	Green
Notta Basal B	Green
IFNg Response	Green
Cholesterol Metabolism	Green
Pentose Phosphate	Green
IFNg Response	Green
IL18-Signaling	Green
ADAM	Green
Regulatory T	Green
IL23-Signaling	Green
OXA Sensitive	Green
Macrophage (M1)	Green
Lipid Metabolism	Green
TIL Signature	Green
IL4-Signaling	Green
Monocytes	Green
Antigen Processing	Green
IL2-Signaling	Green
IL6-Signaling	Green
Th17 Differentiation	Green
IFNg Secretion	Green
Macrophage (M2)	Green
Antigen Processing	Green
IFNg Production	Green
Senescence	Green
Notta Classical B	Green
Moffitt Classical [25]	Green
Hedge Hog-Signaling	Green
Notta Classical A	Green
PI3K Cascade	Green
PD1-Signaling	Green
Ras Pathway	Green
PAC Sensitive	Green
Ox-Phos	Green
Conventional DC	Green
JakStat-Signaling	Green
T-Cell Receptor Signaling	Green
Insulin Signaling	Green
FiveFU Sensitive	Green
NOTCH-Signaling	Green
NFKB Down	Green
IL15-Signaling	Green
Effector T Signature	Green
Moffitt Normal [25]	Green
PI3K Pathway	Green
Retinol Signaling	Green
Sphingolipid-Signaling	Green
EGFR-Signaling	Green
Transendothelial Migration	Green
GEM Signaling	Green
VEGF-Signaling	Green
Rac Pathway	Green

Figure S4 | Distinct TME profiles emerge based on cross compartment phenotypes **a).** Schematic of compartment specific feature extraction used to establish subpopulation proportions and gene signature scores for each patient. **b).** Heatmap represents the correlation matrix across subpopulation proportions. Calculated features were sorted by FPC (*First Principal Component*) ordering. Colored row and column tracks represent the cell compartment used to derive % calculations. *Asterisks represent significance ($p < 0.05$). **c).** Heatmap represents the correlations of cell type specific gene signature score features measured across patients. Features were sorted by FPC (*First Principal Component*) ordering. Colored row and column tracks represent the cell compartment used to derive signature score calculations. The feature group track highlights inclusion within TME phenotypes or pathways pertinent to PDAC (*Interleukins, TGFB, IFNG, Molecular Subtype Signatures, Metabolism, Drug Response*). The 'Signature Length' track is shown at the top representing the # of genes found within each molecular signature. *Asterisks represent significance ($p < 0.05$). Source data are provided as a Source Data file.