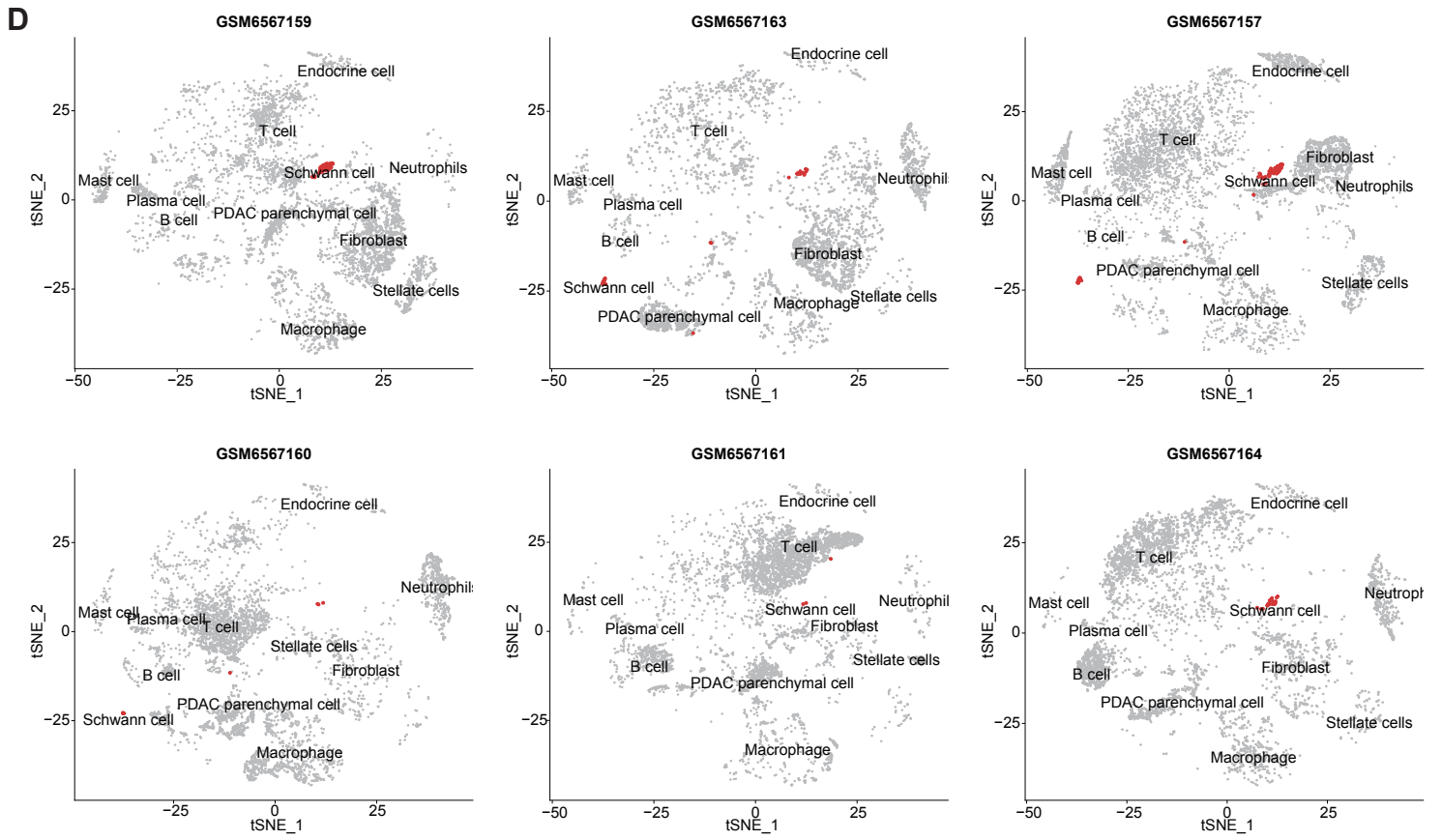
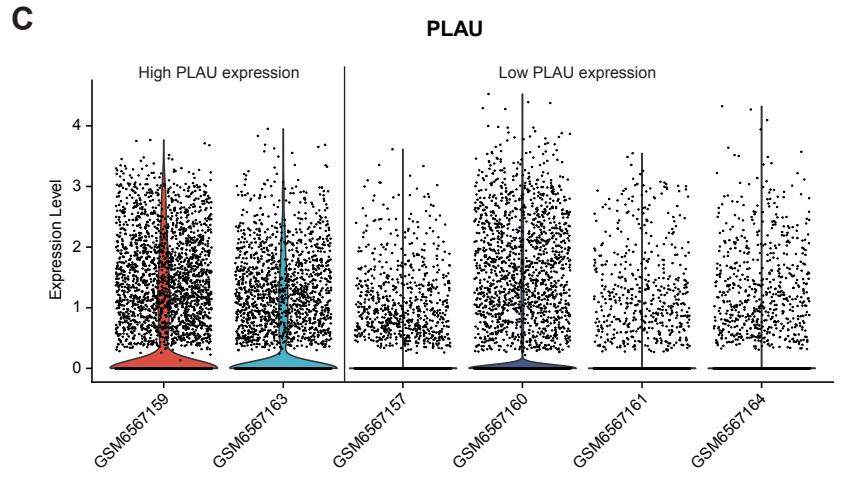
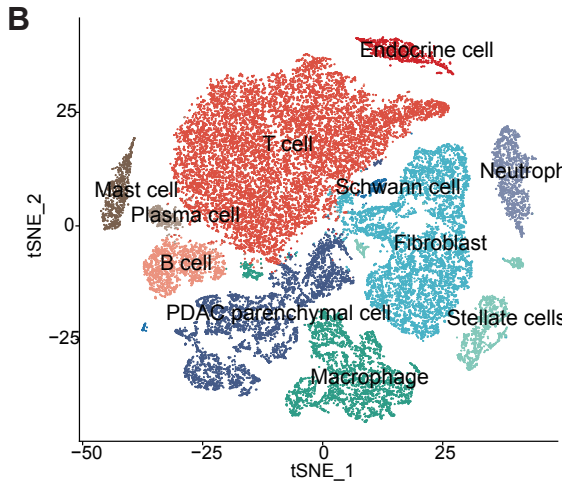
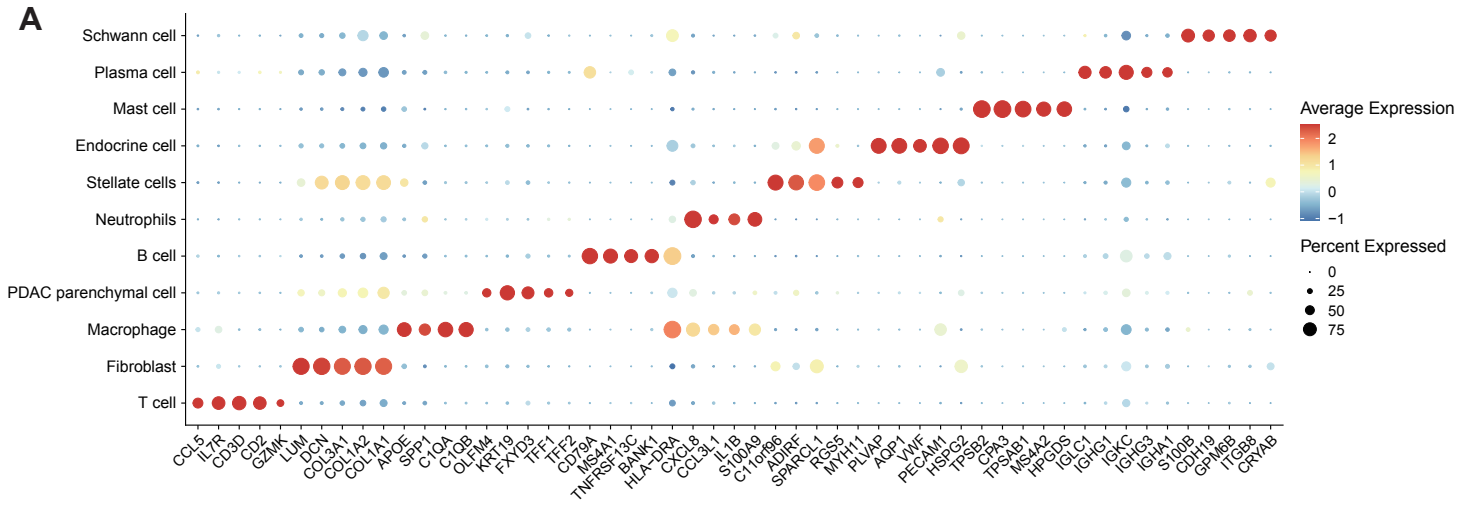


Supplementary Fig. S1 Analyses of RNA expression profiles and Kaplan-Meier survival analysis of key genes in PDAC.

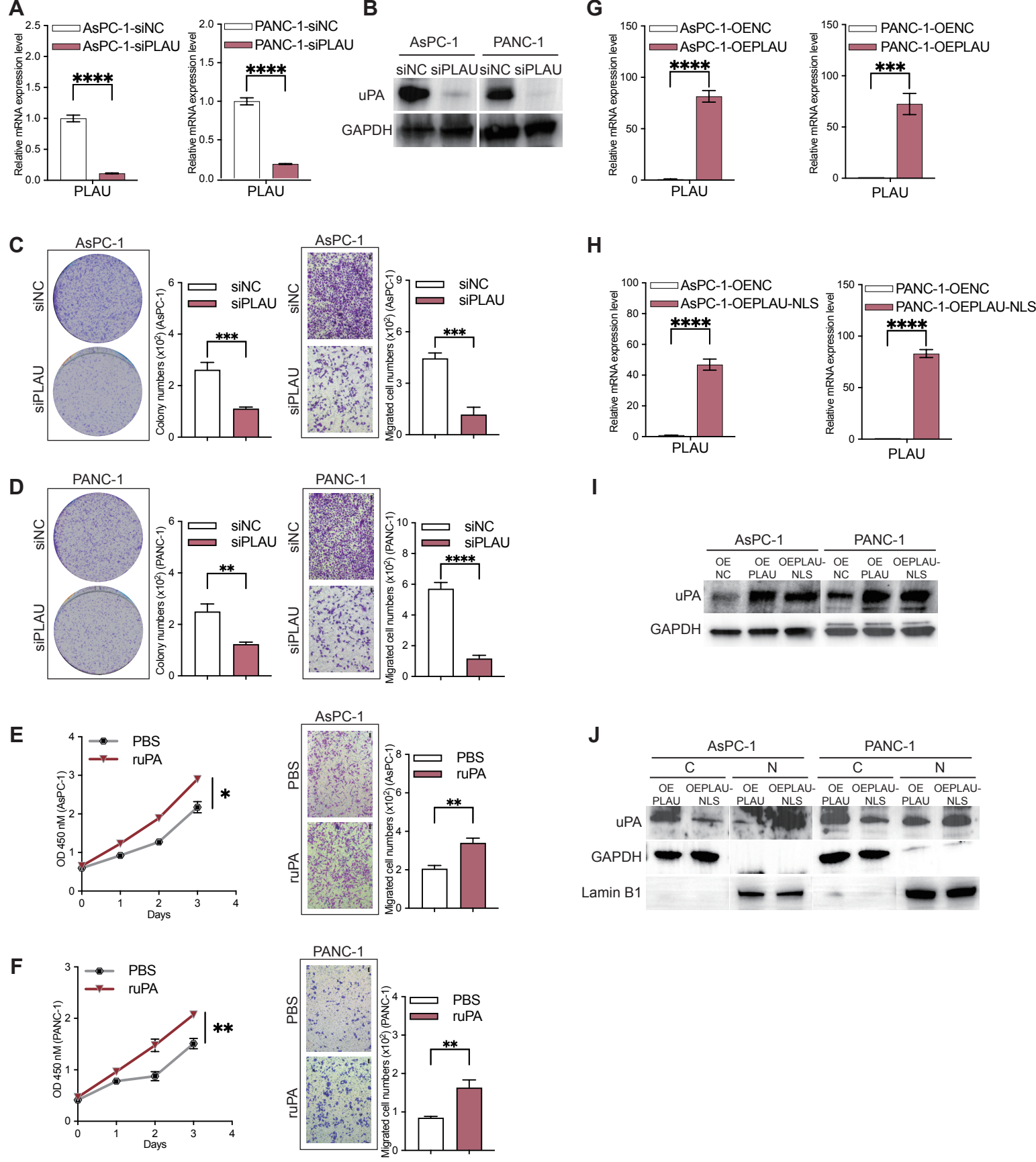
- A. Principal component analyses of differential RNA expression profiles.
- B. Sample clustering and removal of outlier samples. Before quality control (top); after quality control (bottom).

Increasing red color intensity indicates a higher neural invasion velocity.
- C. Analysis of the scale-free index for various soft-threshold powers.
- D. Kaplan-Meier survival curves showed that correlation of gene expression with overall survival (OS) in the TCGA PDAC cohorts (log-rank test, $P < 0.05$).



Supplementary Fig. S2 Cell type classification in pancreatic cancer tumor tissues.

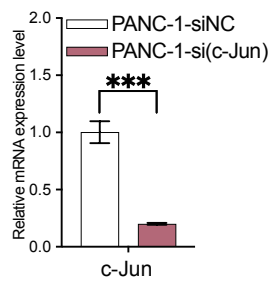
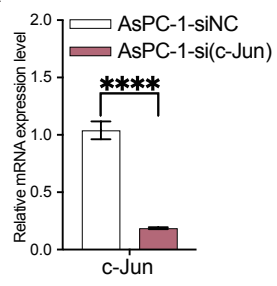
- A. Bubble plot that showed selected cell type-specific markers across all clusters. The size of dots represented the fraction of cells expressing a particular marker, and the intensity of color indicated the level of average expression.
- B. Cell clustering based on cell type-specific markers. Cells were colored according to their corresponding cell type, with distinct colors representing different cell populations.
- C. Violin plots that showed the *PLAU* expression in tumor tissues from 6 pancreatic cancer patients.
- D. t-SNE plots that showed the proportion of Schwann cells in tumor tissues from 6 pancreatic cancer patients.



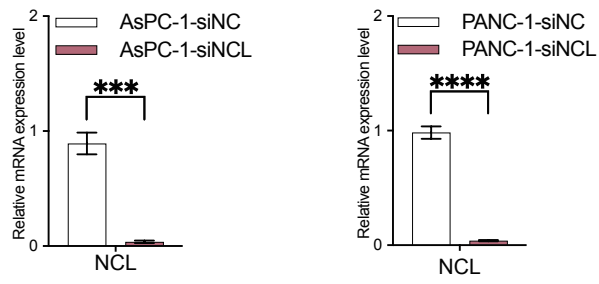
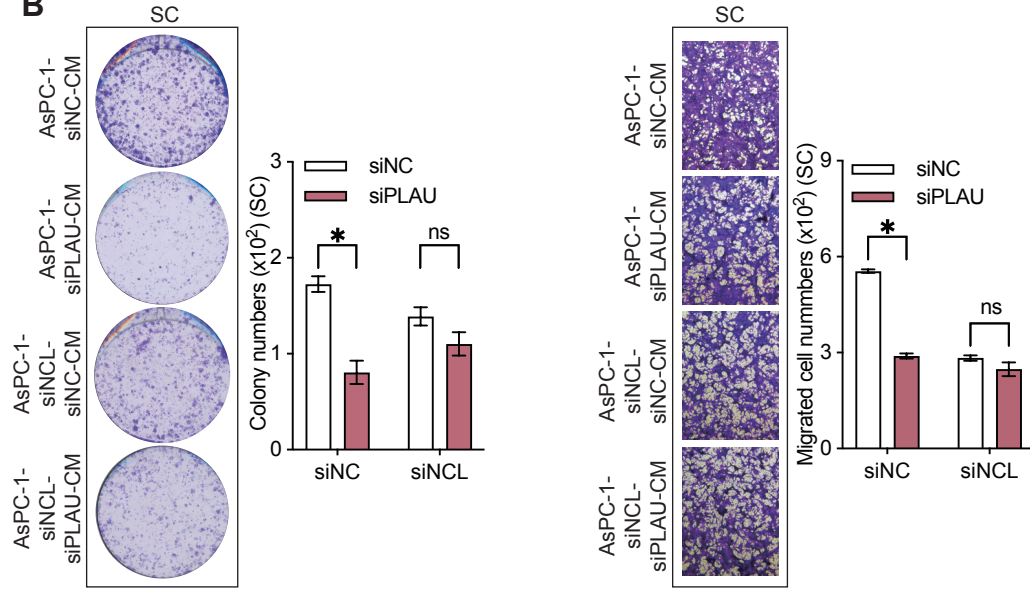
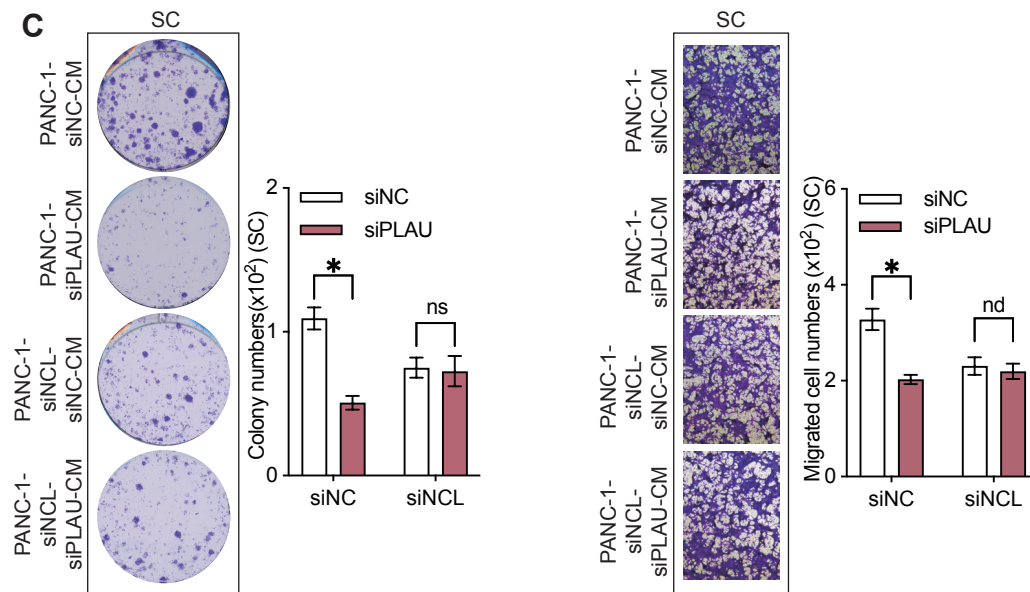
Supplementary Fig. S3 *PLAU* expression and effects on proliferation and migration in PDAC parenchymal cells.

- A. Relative mRNA expression levels of *PLAU* in AsPC-1-siNC cells, AsPC-1-siPLAU cells, PANC-1-siNC cells and PANC-1-siPLAU cells, as detected by qRT-PCR.
- B. uPA levels in AsPC-1-siNC cells, AsPC-1-siPLAU cells, PANC-1-siNC cells and PANC-1-siPLAU cells, detected by Western blots.
- C. Representative microscope images and statistics of colony formation (left) and transwell assay (right) demonstrating AsPC-1-siNC cells' and AsPC-1-siPLAU cells' proliferation and migration capabilities.
- D. Representative microscope images and statistics of colony formation (left) and transwell assay (right) demonstrating PANC-1-siNC cells' and PANC-1-siPLAU cells' proliferation and migration capabilities.
- E. Cell proliferation (left) and representative microscope images and statistics of transwell assay (right) demonstrating AsPC-1 cells' proliferation and migration capabilities after treatment with PBS, recombinant uPA protein (ruPA).
- F. Cell proliferation (left) and representative microscope images and statistics of transwell assay (right) demonstrating PANC-1 cells' proliferation and migration capabilities after treatment with PBS, recombinant uPA protein (ruPA).
- G. Relative mRNA expression levels of *PLAU* in AsPC-1-OENC cells, AsPC-1-OEPLAU cells, PANC-1-OENC cells and PANC-1-OEPLAU cells, as detected by qRT-PCR.
- H. Relative mRNA expression levels of *PLAU* in AsPC-1-OENC cells, AsPC-1-OEPLAU-NLS cells, PANC-1-OENC cells and PANC-1-OEPLAU-NLS cells, as detected by qRT-PCR.
- I. uPA levels in AsPC-1-OENC cells, AsPC-1-OEPLAU cells, AsPC-1-OEPLAU-NLS cells, PANC-1-OENC cells, PANC-1-OEPLAU cells and PANC-1-OEPLAU-NLS cells, detected by Western blots.
- J. uPA levels in cytosolic (C) and nuclear (N) fractions of AsPC-1-OEPLAU cells, AsPC-1-OEPLAU-NLS cells, PANC-1-OEPLAU cells and PANC-1-OEPLAU-NLS cells, detected by Western blots. GAPDH and lamin B1 were shown as markers of the cytoplasm and nucleus respectively.

(A, C-H) Two-sided T-test was used to calculate statistical significance ($*P < 0.05$; $**P < 0.01$; $***P < 0.001$; $****P < 0.0001$, ns non-significant).

A

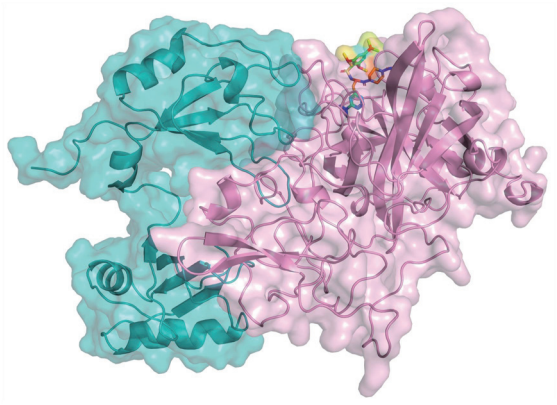
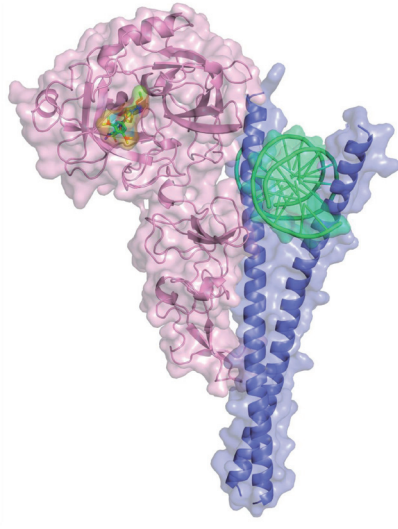
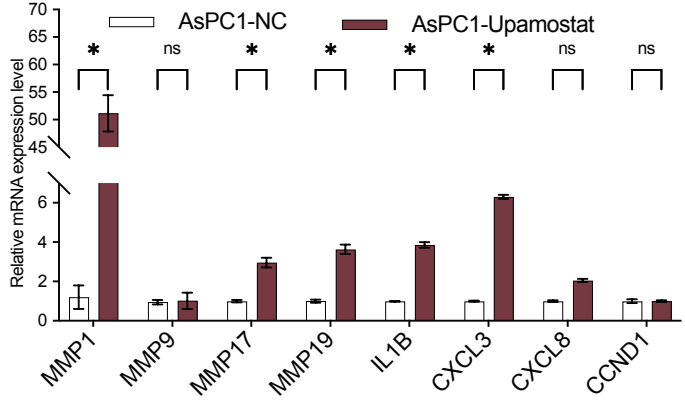
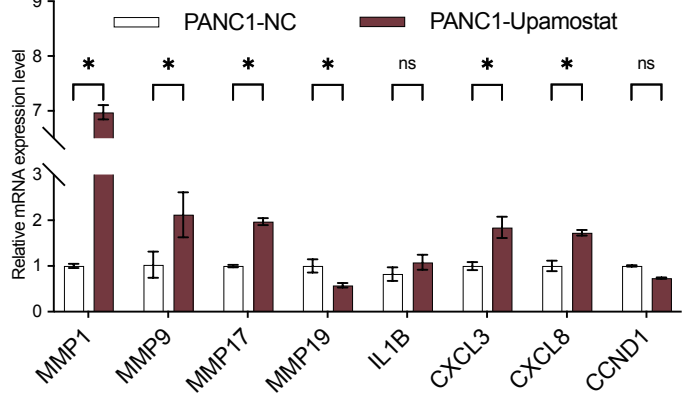
Supplementary Fig. S4 Relative mRNA expression levels of *c-Jun* in AsPC-1-siNC cells, AsPC-1-si(*c-Jun*) cells, PANC-1-siNC cells and PANC-1-si(*c-Jun*) cells, as detected by qRT-PCR.

A**B****C**

Supplementary Fig. S5 The conditioned medium from NCL and PLAU knockdown in PDAC parenchymal cells modulated Schwann cell proliferation and migration.

- A. Relative mRNA expression levels of *Nucleolin* (*NCL*) in AsPC-1-siNC cells, AsPC-1-siNucleolin(*NCL*) cells, PANC-1-siNC cells and PANC-1-siNCL cells, as detected by qRT-PCR.
- B. Representative microscope images and statistics of colony formation (left) and transwell assay (right) demonstrating SCs' proliferation and migration capabilities after treatment with CM from AsPC-1-siNC cells, CM from AsPC-1-siPLAU cells, CM from AsPC-1-siNCL-siNC cells and CM from AsPC-1-siNCL-siPLAU cells.
- C. Representative microscope images and statistics of colony formation (left) and transwell assay (right) demonstrating SCs' proliferation and migration capabilities after treatment with CM from PANC-1-siNC cells, CM from PANC-1-siPLAU cells, CM from PANC-1-siNCL-siNC cells and CM from PANC-1-siNCL-siPLAU cells.

(A-G) Two-sided T-test was used to calculate statistical significance ($*P < 0.05$; $**P < 0.01$; $***P < 0.001$; $****P < 0.0001$, ns non-significant).

A**B****C****D**

Supplementary Fig. S6 Upamostat, a uPA-targeting small-molecule inhibitor, did not suppress uPA's c-Jun-dependent transcriptional regulation.

- A. Three-dimensional representation of the interaction among uPA, NCL, and Upamostat (deep green, NCL; pink, uPA; rainbow, Upamostat;).
- B. Three-dimensional representation of the interaction among c-Jun, motif, uPA, and Upamostat (deep blue, c-Jun; deep green, DNA motif; pink, uPA; rainbow, Upamostat;).
- C. Relative mRNA expression levels of MMPs, IL1B, CXCLs and CCND1 in AsPC-1 cells supplemented with vehicle (NC) or Upamostat, as detected by qRT-PCR.
- D. Relative mRNA expression levels of MMPs, IL1B, CXCLs and CCND1 in PANC-1 cells supplemented with vehicle (NC) or Upamostat, as detected by qRT-PCR.

(C-D) Two-sided T-test was used to calculate statistical significance (*P < 0.05; **P < 0.01; ***P < 0.001; ****P < 0.0001, ns non-significant).