

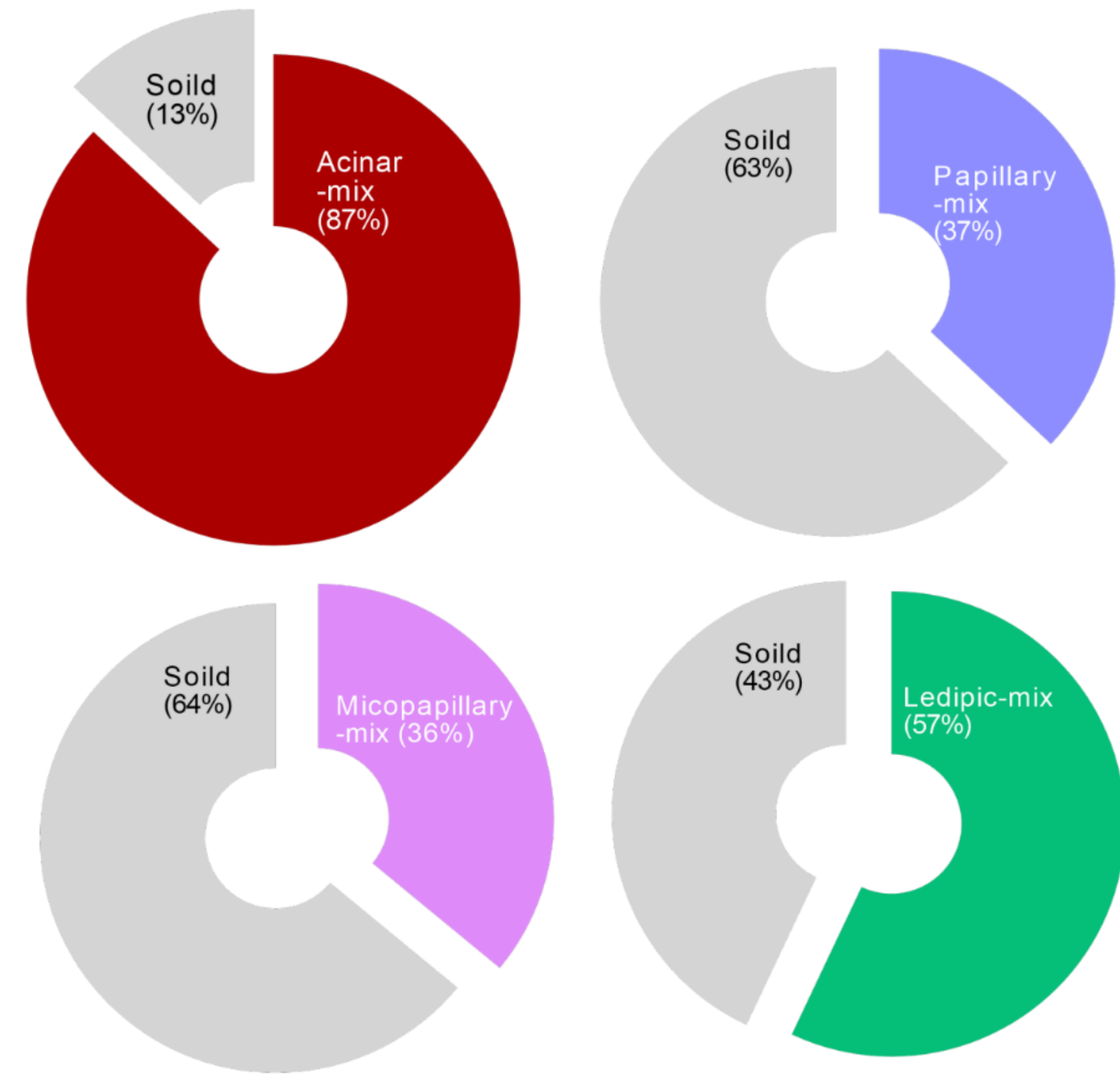
P2.036 TSPAN8-ITGA4 Axis Drives CAF-Mediated Acinar-to-Solid Transition in Lung Adenocarcinoma

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IASLC 2026 World
Conference on Lung Cancer
SEPTEMBER 12 – 15, 2026
SEOUL, REPUBLIC OF KOREA

Introduction

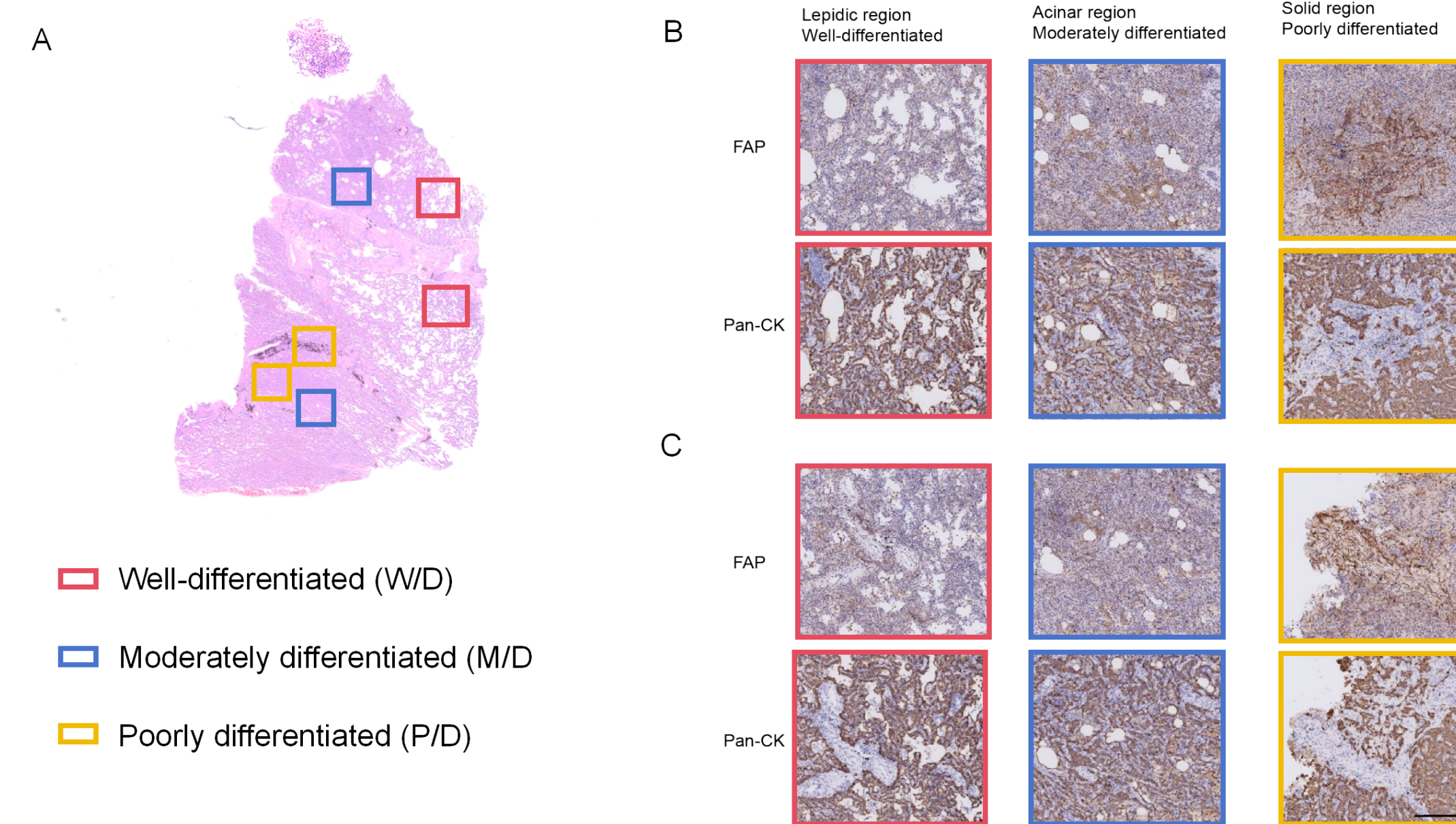
The morphological evolution from acinar to solid patterns represents a critical malignant progression in lung adenocarcinoma (LUAD), yet the underlying microenvironmental mechanisms remain poorly understood. Tetraspanin-8 (TSPAN8), a key organizer of membrane microdomains, and integrin $\alpha 4$ (ITGA4), a mechanosensitive adhesion receptor, have emerged as potential mediators of tumor-stroma crosstalk.



Pie charts illustrating the distribution of histological patterns in lung adenocarcinoma specimens. Each chart represents an individual patient sample, showing the proportion of solid (red), acinar (blue), lepidic (green), papillary (purple), and micropapillary (pink) patterns. Notably, solid and acinar patterns frequently coexist within the same tumor, with solid-acinar mixed patterns observed in the majority of cases (upper left and upper right). Pure solid (lower left) or pure lepidic (lower right) patterns are less common. This morphological heterogeneity suggests dynamic transitions between acinar and solid architectures during tumor progression, highlighting the clinical relevance of understanding microenvironmental drivers of pattern evolution.

Methods

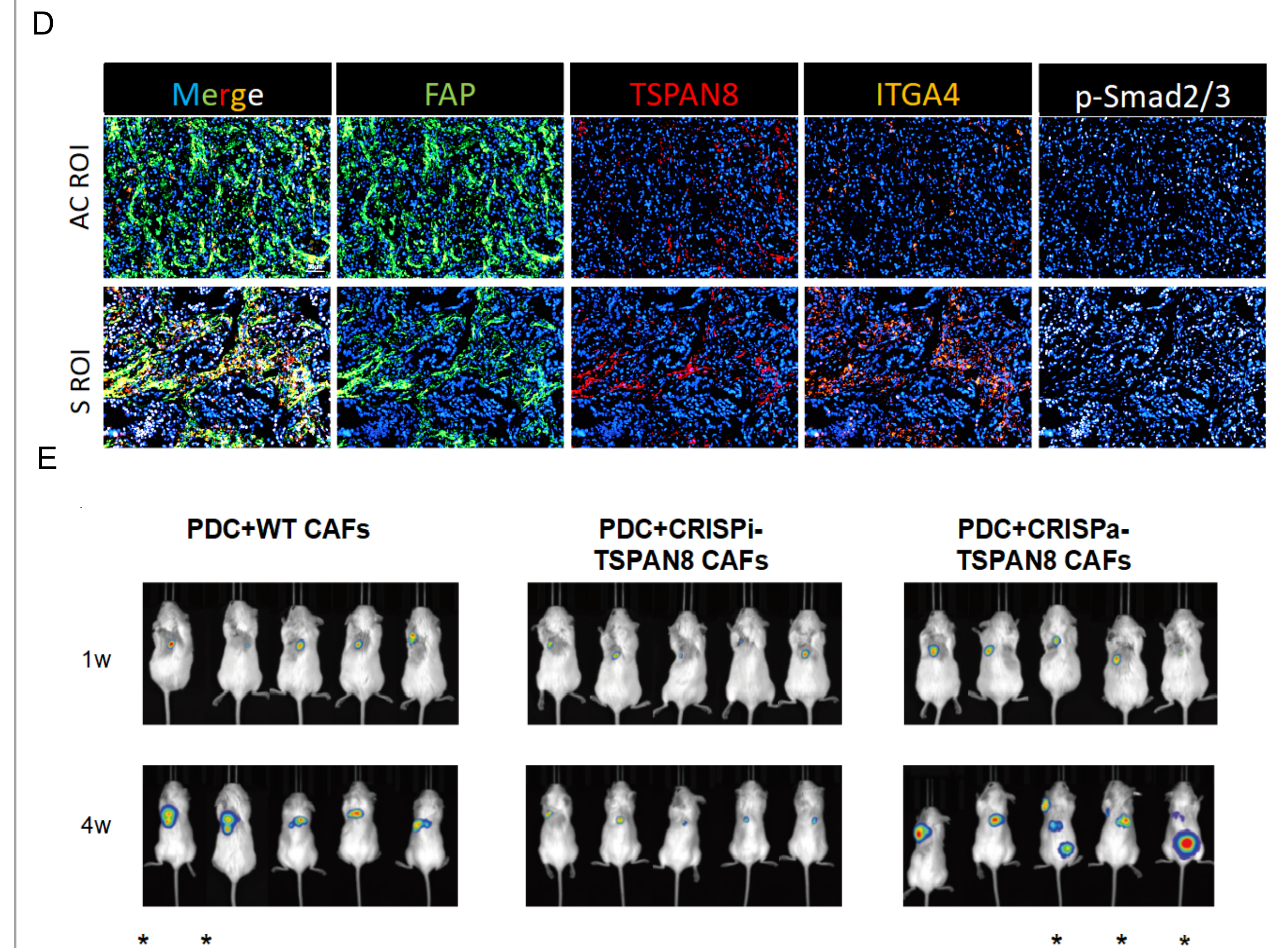
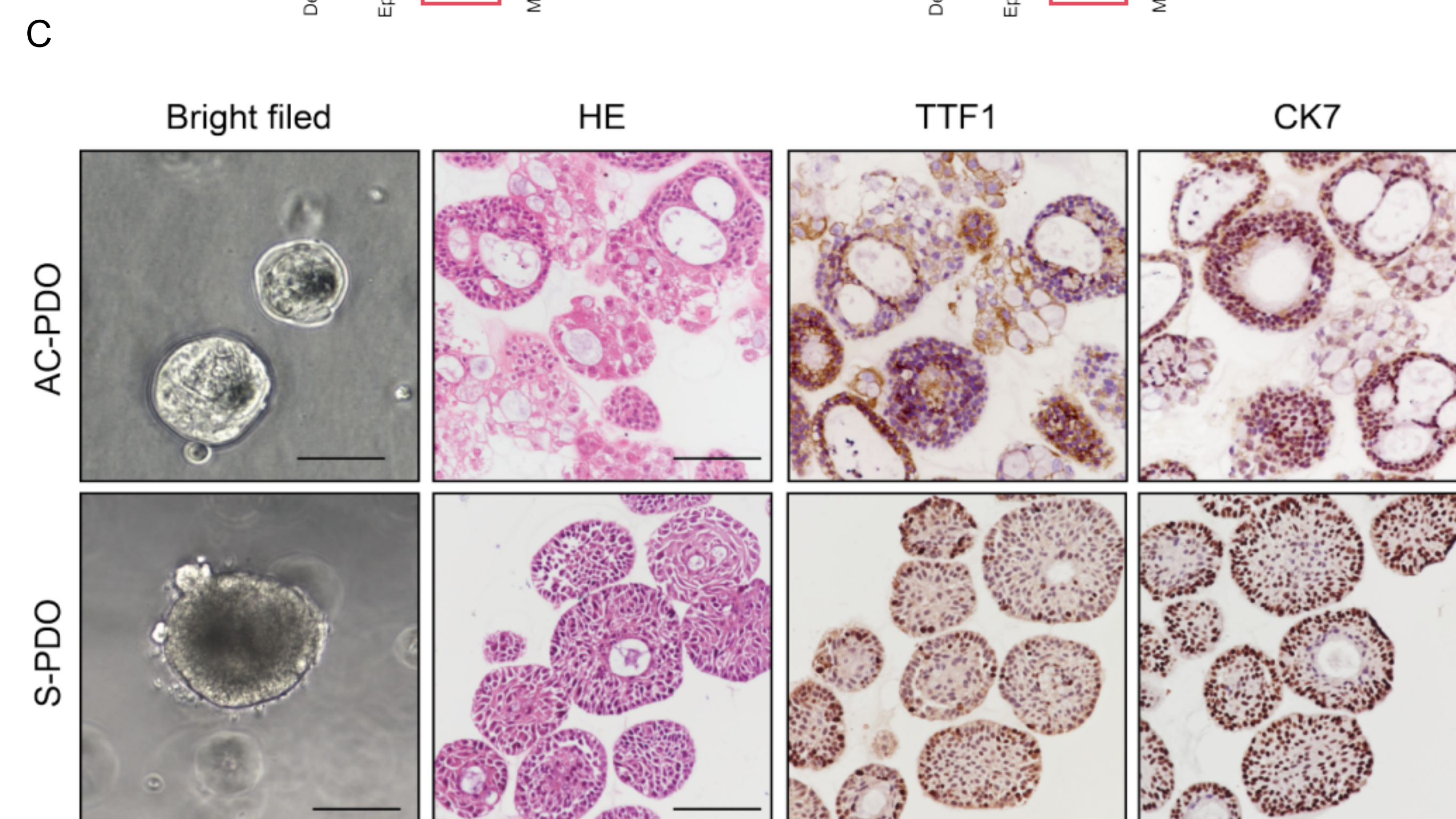
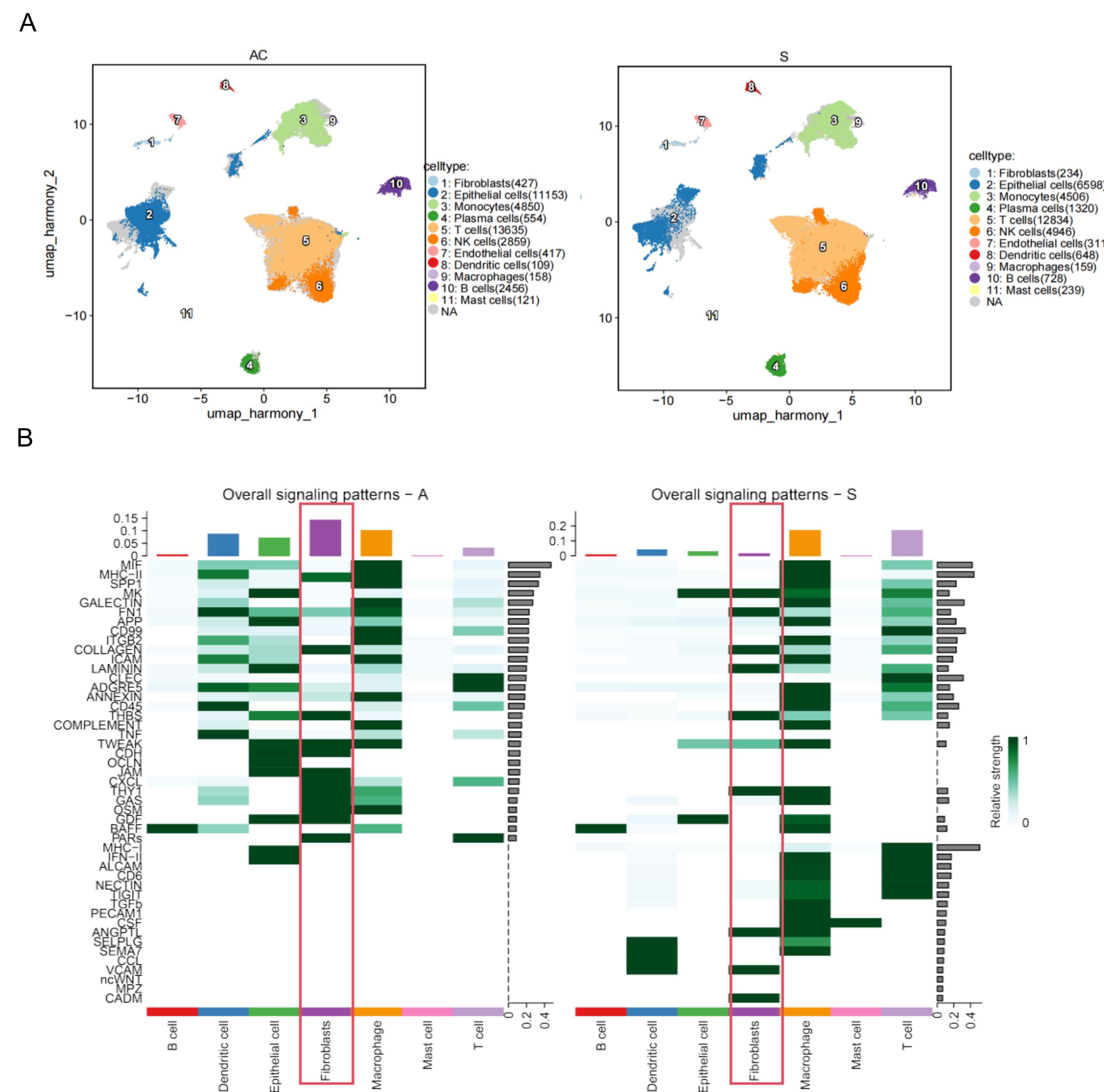
We integrated single-cell RNA sequencing (scRNA-seq) with laser capture microdissection-based proteomics (LCM-proteomics) to identify the TSPAN8-ITGA4 axis as a critical mediator of CAF-tumor cell communication. Functional validation was performed through overexpression and knockdown experiments in CAFs and tumor cells in vitro, followed by patient-derived organoid (PDO) and patient-derived organoid xenograft (PDOX) models to assess morphological and behavioral changes.



(A) Representative H&E-stained lung adenocarcinoma tissue section with annotated regions of interest (ROIs). Purple boxes indicate well-differentiated acinar regions (WD), blue boxes denote moderately differentiated acinar regions (MD), and orange boxes mark poorly differentiated solid regions (PD).
(B-C) High-magnification views of selected ROIs before (B) and after (C) laser capture microdissection (LCM). Cell segmentation was performed using QuPath integrated with CellPose and Segment Anything Model (SAM) to precisely delineate individual cells within each histological pattern. Microdissected regions (highlighted in orange boxes in C) were subjected to mass spectrometry-based proteomics to profile pattern-specific protein expression.

Results

Integration of scRNA-seq and LCM-proteomics revealed enrichment of TSPAN8+ CAFs at the invasive front, physically interacting with ITGA4+ tumor cells in solid-pattern regions. Genetic manipulation of TSPAN8 in CAFs or ITGA4 in tumor cells significantly reversed solid-pattern formation and restored acinar polarity in both PDO and PDOX models. Mechanistically, TSPAN8-ITGA4 engagement activated TGF- β /Smad signaling and cytoskeletal remodeling, driving apicobasal polarity disruption and collective migration.



(A) UMAP visualization of single-cell RNA sequencing (scRNA-seq) data from acinar (AC, left) and solid (S, right) pattern lung adenocarcinoma specimens. Cell clusters are color-coded by cell type, including epithelial cells (orange), fibroblasts (green), endothelial cells (blue), T cells (light blue), B cells (purple), myeloid cells (pink), and mast cells (gray). Solid-pattern tumors exhibit distinct clustering of cancer-associated fibroblasts (CAFs) compared to acinar-pattern tumors.

(B) Cell-cell interaction strength heatmaps comparing overall signaling patterns between acinar (A, left) and solid (S, right) regions. Red boxes highlight significantly enhanced tumor-CAF interactions in solid-pattern regions, particularly involving fibroblast-derived signaling pathways. Solid tumors display stronger CAF-epithelial crosstalk compared to acinar tumors, suggesting microenvironmental remodeling during morphological transition.

(C) Patient-derived organoid (PDO) models recapitulate acinar (AC-PDO, upper) and solid (S-PDO, lower) morphological features. Bright-field images show distinct architectural differences: AC-PDOs exhibit hollow, polarized acinar structures, while S-PDOs display compact, solid morphology. H&E staining, TTF1 (thyroid transcription factor 1, epithelial marker), and CK7 (cytokeratin 7, luminal marker) immunohistochemistry confirm preservation of pattern-specific characteristics in vitro. Scale bars: 100 μ m.

(D) Multiplex immunohistochemistry (mIHC) validation of TSPAN8-ITGA4 axis at the acinar-solid interface. Upper panels (AC ROI) show acinar regions with low TSPAN8 (red) and ITGA4 (yellow) expression. Lower panels (S ROI) demonstrate enrichment of TSPAN8+ CAFs (co-localized with FAP, green) and ITGA4+ tumor cells at the invasive front of solid regions. p-Smad2/3 (cyan) activation is elevated in solid regions, indicating active TGF- β signaling

Conclusion

Our findings establish the TSPAN8-ITGA4 physical axis as a novel driver of CAF-mediated morphological reprogramming in LUAD. Targeting this axis may offer therapeutic strategies to prevent early-stage malignant progression and improve patient outcomes.

Funding: This work was supported by the Postdoctoral Fellowship Program of CPSF (Grant No. GZC20251396); the Post-Doctor Research Project, West China Hospital, Sichuan University (Grant No. 2025HXBH092).