



P3.162: A POSTN-Centered Stiffness Niche Drives Solid-Component Progression in mGGO Lung Adenocarcinoma

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INTRODUCTION

Mixed ground-glass opacity (mGGO) lung adenocarcinoma contains spatially distinct ground-glass and solid components within the same lesion. The solid component is associated with greater invasive potential, yet the biological basis of this intratumoral heterogeneity remains unclear. Accurate paired regional analysis is technically challenging because CT attenuation, gross appearance, tissue stiffness and histopathology represent related but non-equivalent properties. We hypothesized that CAF-mediated matrix remodeling generates a POSTN-centered stiffness niche that promotes solid-component progression through tumor-cell mechanotransduction.

METHODS

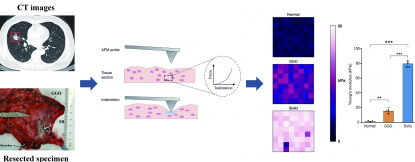
Radiology-guided paired sampling

Preoperative thin-section CT and three-dimensional bronchovascular reconstruction were used to map ground-glass- and solid-dominant regions relative to anatomical landmarks. After resection, specimens were anatomically oriented, opened along the predicted lesion plane and serially sectioned. Candidate regions were selected by integrating spatial correspondence, gross appearance and palpated stiffness, followed by histopathological assessment.

Multi-scale characterization

Atomic force microscopy quantified tissue stiffness in 12 paired lesions. Paired bulk RNA sequencing was performed in 14 lesions, single-cell RNA sequencing in 5 paired specimens and spatial transcriptomics in 3 paired specimens. Cell-cell communication analysis, tunable-stiffness culture and fibroblast-tumor co-culture models were used for mechanistic investigation. An independent tissue microarray cohort of 114 patients was used for clinical validation.

REGIONAL STIFFNESS MEASUREMENT



DISCUSSION AND CONCLUSION

Mechanistic interpretation

Our findings support a model in which POSTN-high CAFs remodel the extracellular matrix and generate a stiffness niche accompanied by coordinated PIEZO1 and YAP/TAZ-associated responses in tumor cells. This stiffness-responsive stromal-epithelial program provides a biological explanation for solid-component progression in mGGO lung adenocarcinoma.

Why sampling matters

The biological model is supported by multi-modal evidence, but its interpretation ultimately depends on the accuracy of regional radiology-pathology registration.

Take-home message

A POSTN-high CAF-mediated stiffness niche promotes solid-component progression through stiffness-responsive signaling involving PIEZO1 and YAP/TAZ.

Next step

The next advance may come not from another sequencing platform, but from knowing exactly what we have sampled.

SELECTED REFERENCES

- He Y, et al. Single-cell RNA sequencing unravels distinct tumor microenvironments of different components of lung adenocarcinoma featured as mixed ground-glass opacity. *Front Immunol.* 2022;13:903513.
- Takatsu F, et al. Periostin secreted by cancer-associated fibroblasts promotes cancer progression and drug resistance in non-small cell lung cancer. *J Mol Med (Berl).* 2023;101:1603-1614.
- Park Y, et al. The matrix stiffness coordinates cell proliferation and PD-L1 expression via YAP in lung adenocarcinoma. *Cancers (Basel).* 2024;16:598.

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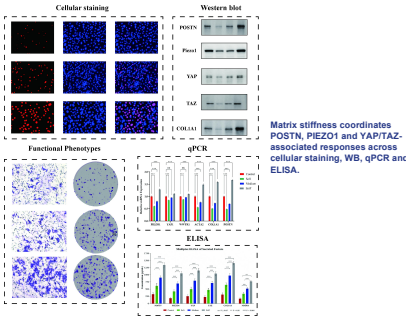
RESULTS | DID WE SAMPLE THE RIGHT REGION?

WHAT OUR CURRENT DATA SHOW

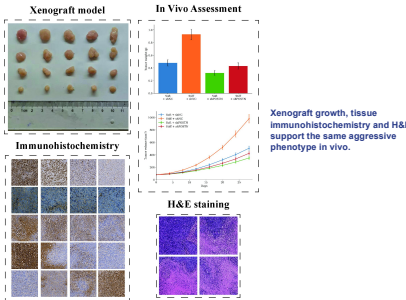
Mechanism A POSTN-centered stiffness-responsive program involving PIEZO1 and YAP/TAZ.

Validation Concordant in vitro, in vivo, tissue and clinical associations.

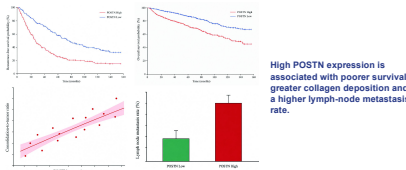
1 MECHANISM / FUNCTION



2 IN VIVO / TISSUE VALIDATION



3 CLINICAL ASSOCIATION



Mechanistic evidence → in vivo/tissue validation → clinical relevance

THE PROBLEM WE NEED TO SOLVE

CT attenuation does not equal histology

GGO blends into aerated lung, while deflation, manipulation and sectioning distort the geometry seen on CT.

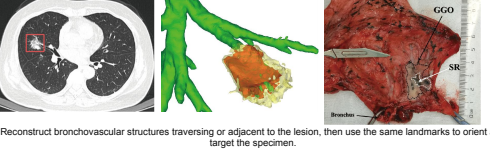
Multiple clues, no accepted gold standard

Anatomical landmarks, gross layering, needle localization and stiffness can complement one another—but none independently proves the match.

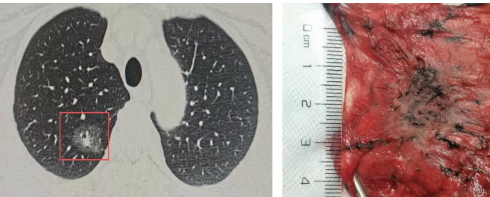
CAN WE PROSPECTIVELY MEASURE REGISTRATION ERROR?

CANDIDATE PRE-SAMPLING LOCALIZATION STRATEGIES

1 Bronchovascular landmark-based localization

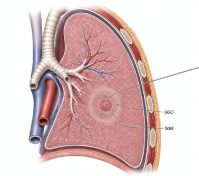


2 Gross layering-based identification



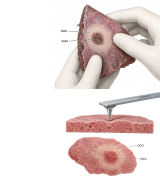
Expose natural GGO-solid layering by transverse or longitudinal sectioning and directly compare the two components.

3 Needle-guided localization



For deep nodules, the needle tip can serve as an intraoperative anatomical reference.

4 Stiffness-assisted identification



Use gross stiffness as a rapid clue and AFM as a quantitative mechanical measurement.

None of these cues alone proves radiology-histology correspondence.

HOW WOULD YOU VALIDATE THE MATCH?

Ex vivo specimen imaging • patient-specific cutting guides
quantitative stiffness mapping • three-dimensional pathology