



Multi-Omics Integration Identifies CDH3-Driven Malignant Progression and Pathology-Based Risk Stratification in Thymic Epithelial Tumors

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INTRODUCTION

Thymic epithelial tumors (TETs) are rare and highly heterogeneous malignancies with marked variation in biological behavior and clinical outcome. However, the malignant epithelial states that drive aggressive progression remain poorly defined.

Beyond tumor-intrinsic heterogeneity, how aggressive epithelial states are spatially organized and interact with the surrounding immune-stromal microenvironment is still incompletely understood.

OBJECTIVE Identify a CDH3-associated aggressive malignant epithelial state, characterize its immune-stromal niche and therapeutic vulnerabilities, and determine whether its molecular phenotype can be captured from routine H&E images for pathology-based risk stratification.

METHODS

- Multi-omic discovery**
Single-cell RNA sequencing, spatial transcriptomics, multiplex immunofluorescence, and bulk transcriptomics.
- State and ecosystem inference**
copyKAT; Scissor, CytoTRACE and trajectory inference; SCENIC; CellChat/NicheNet; hdWGCNA and NMF subtyping.
- Functional and therapeutic validation**
CDH3 knockdown, proliferation and migration assays, drug-sensitivity analysis, xenografts, and patient-derived organoids.
- Computational pathology**
Weakly supervised CLAM multiple-instance learning on routine H&E whole-slide images to predict CDH3-associated molecular subgroups.

Integrated outputs: malignant state, niche interactions, genomic risk, candidate agents, and a pathology-derived score.

DISCUSSION AND CONCLUSION

TAKE-HOME MESSAGE

CDH3 links malignant epithelial plasticity to an immunosuppressive niche and provides a **biomarker, therapeutic entry point, and pathology-derived risk signal**.

- Malignant state:** CDH3-positive cells were stem-like, pro-invasive, and enriched for EMT-related programs.
- Tumor ecosystem:** CDH3-high tumors were associated with M2 macrophage-, CAF-, TGF-beta-, and EMT-rich microenvironments.
- Mechanistic axis:** CCN2-LRP1 was prioritized as a candidate epithelial-myeloid interaction pathway.
- Translational value:** CDH3 perturbation, candidate drugs, and routine H&E modeling converged on a clinically relevant high-risk state.

FUTURE DIRECTION

Prospective multicenter validation of the pathology score and preclinical testing of CDH3-directed combination strategies are warranted.

STUDY AT A GLANCE

MULTI-LEVEL EVIDENCE

51,463 single cells	117 TCGA-THYM Cases	91 mIF samples
32 in-house cases	2 Candidate Agents	0.79 test-set AUC

TRANSLATIONAL PATHWAY

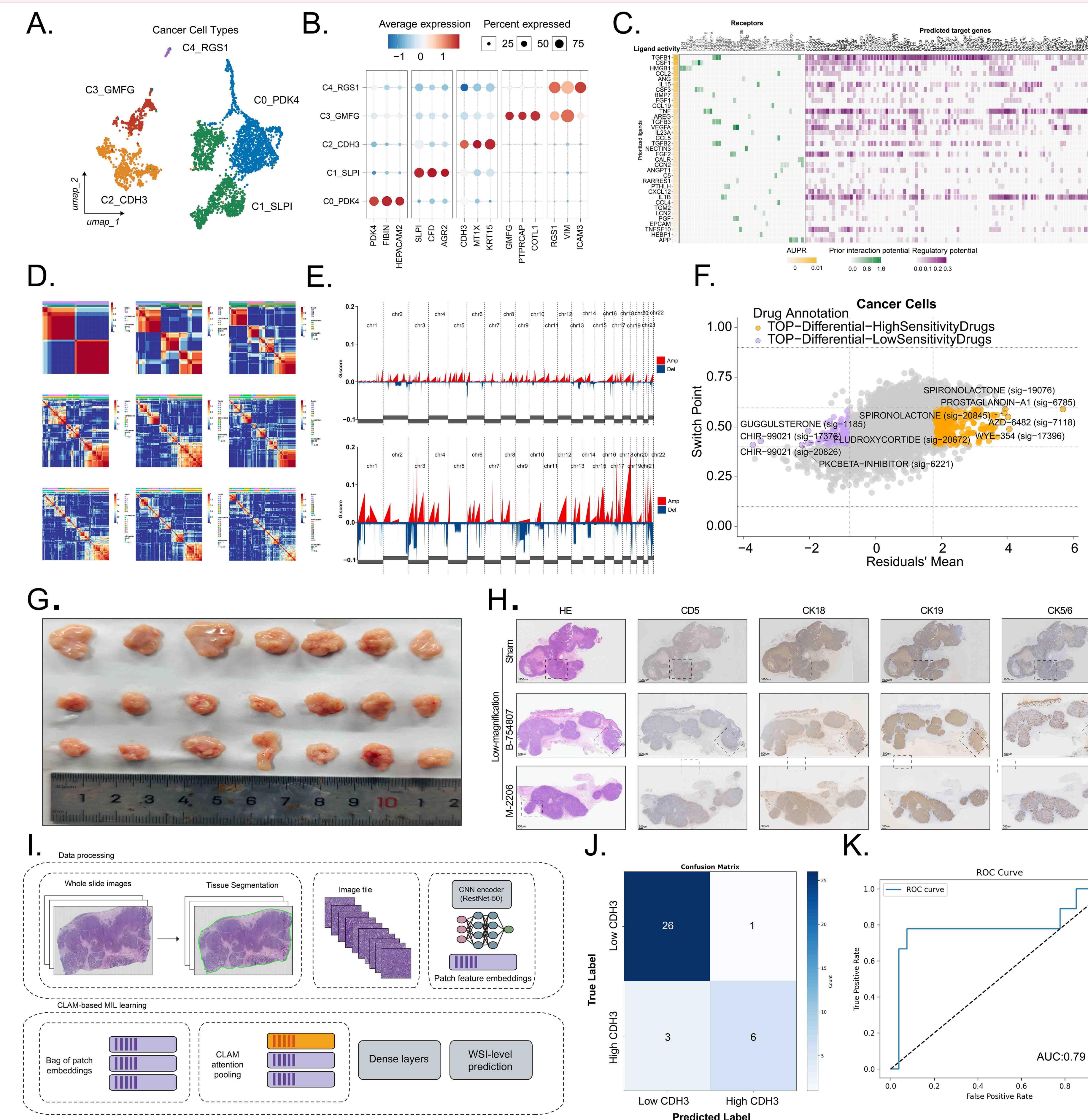


single-cell + spatial multi-omics + function routine pathology

AI USE ChatGPT (OpenAI) was used for English-language polishing and poster layout refinement. All scientific content, analyses, interpretations, and final wording were reviewed and approved by the authors.

RESULTS

- CDH3 state:** stem-like, pro-invasive, and EMT-enriched.
- Therapy:** CDH3 knockdown and BMS-754807/MK-2206 suppressed malignant phenotypes.
- Niche:** M2 macrophage/fibroblast-rich with CCN2-LRP1 signaling.
- Pathology AI:** routine H&E predicted CDH3-associated risk (AUC 0.79).



Integrated validation of CDH3-driven malignant progression. (A-B) malignant epithelial states and markers; (C-D) interaction and molecular programs; (E) genomic instability; (F-H) drug prioritization and in vivo/pathologic validation; (I-K) CLAM-based H&E model and performance.