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Summary

MULTI-RESOLUTION SPATIAL TRANSCRIPTOMICS REVEALS CELL-LEVEL INVASION MECHANISMS AND DRUGGABLE TARGETS IN INTRADUCTAL PAPILLARY MUCINOUS NEOPLASMS OF THE PANCREAS

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Multi-resolution spatial transcriptomics of intraductal papillary mucinous neoplasms identified two distinct cellular invasion programs and 26 actionable therapeutic targets including TROP2-directed and CXCR4-targeted agents.

KEY POINTS

- Analysis of 22 Visium and 4 VisiumHD libraries from 15 IPMN cases revealed two parallel invasion programs: a protease-driven program (MMP7/CD55/SLC2A1) and a partial EMT program (SPARC/COL1A1/VIM), detectable only at cellular resolution.
- Pseudotime analysis showed progression from MUC5AC+/MUC2+ goblet-like cells to MMP7+/CD55+ invasive-epithelial cells, with a 7.4-fold decrease in MUC5AC and 16-fold increase in MMP7.
- Flat-type high-grade lesions were molecularly closer to invasive regions while mural nodules occupied a divergent branch, supporting distinct progression routes.
- Four microenvironmental phenotypes were defined, with iCAF proximity under 100 µm associated with M1 macrophage polarization and consistent CXCL12-CXCR4 signaling across samples.
- Druggability analysis identified 26 clinically relevant candidates including sacituzumab govitecan (TROP2-directed ADC), plerixafor (CXCR4 antagonist), and simtuzumab (LOXL2 inhibitor), highlighting case-specific therapeutic vulnerabilities.

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