

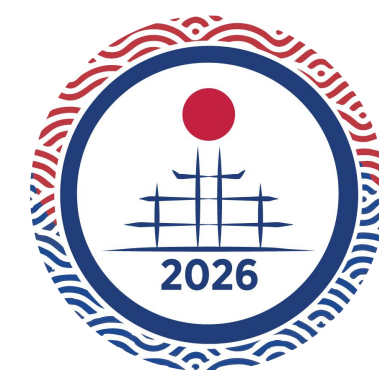


P3.068: Spatial and Single-Cell Profiling Uncovers Matrix-Remodeling Pericyte–MMP14⁺ Capillary Endothelial Cell Crosstalk Fuels Metastatic Propensity in Non-Small Cell Lung Cancer

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INTRODUCTION

Distant metastasis remains a major cause of poor outcomes in non-small cell lung cancer (NSCLC). Pericytes are key components of the vascular microenvironment, yet tumor-associated pericytes are functionally heterogeneous and may either suppress or promote metastatic progression.

Emerging evidence suggests that specific pericyte states can remodel the perivascular extracellular matrix (ECM) and facilitate tumor dissemination. However, their heterogeneity, spatial organization, and endothelial interactions in NSCLC remain poorly defined.

Here, we integrated pericyte-focused single-cell RNA sequencing with Xenium spatial transcriptomics to characterize metastasis-associated pericyte states and their spatial crosstalk within the NSCLC vascular microenvironment.

METHODS

Pericytes isolated from NSCLC tumor and adjacent normal tissues were subjected to single-cell RNA sequencing (scRNA-seq) to characterize pericyte heterogeneity and define distinct cellular states. An independent Xenium spatial transcriptomic cohort of metastatic and non-metastatic NSCLC samples was used to map pericyte subpopulations and their spatial organization within the tumor microenvironment.

Functional enrichment, pseudotime trajectory, and differential abundance analyses were performed to characterize pericyte states. Spatial niche analysis, cell–cell proximity assessment, and ligand–receptor inference were further applied to investigate spatial and molecular interactions between pericytes and endothelial cells. Key spatial findings were validated by multiplex immunofluorescence.

Public single-cell and bulk transcriptomic datasets were additionally integrated for external validation, survival analysis, and development of a matPC-associated metastasis risk model using propensity score matching and LASSO regression.

REFERENCES & ACKNOWLEDGEMENTS

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RESULTS

Single-Cell and Spatial Profiling Reveals matPC Enrichment in Metastatic Vascular Niches

Single-cell profiling identified four distinct pericyte populations, including matrix-remodeling pericytes (matPCs), vasodilatory pericytes (vdPCs), myogenic pericytes (myoPCs), and proliferating pericytes (proPCs), with matPCs preferentially expanded in tumor tissues. Xenium spatial transcriptomics further revealed that matPCs were predominantly localized within vasculature-enriched niches. Notably, the proportion of matPCs within these vascular niches was significantly higher in metastatic than in non-metastatic NSCLC ($p = 0.034$). Consistently, matPCs exhibited the highest metastasis-associated gene score among pericyte subsets, supporting their close association with metastatic progression.

Single-Cell sequencing cohort

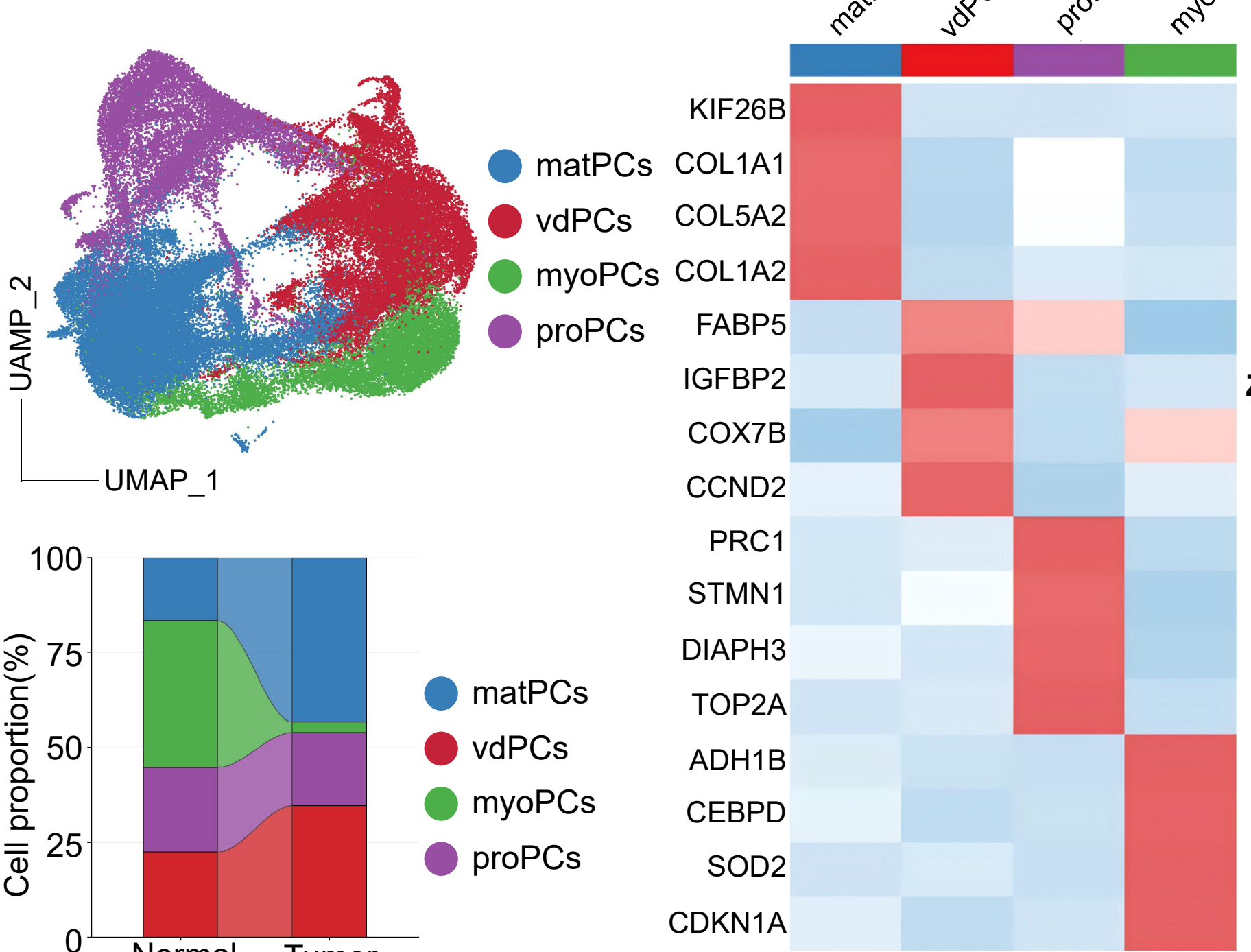


Figure1. Single-cell and spatial profiling reveals pericyte heterogeneity and selective enrichment of matrix-remodeling pericytes (matPCs) within vascular niches of metastatic NSCLC.

Xenium Spatial cohort

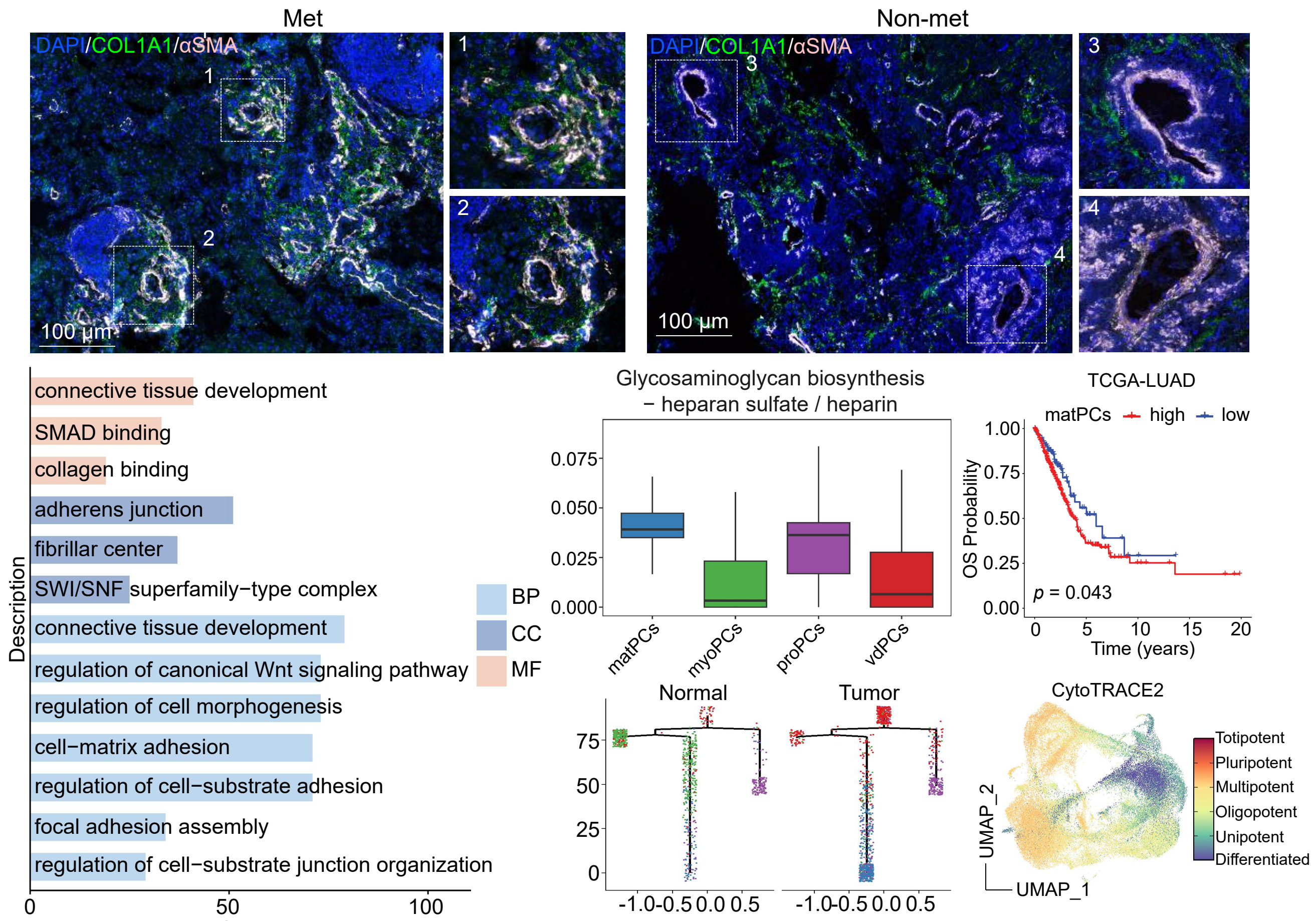
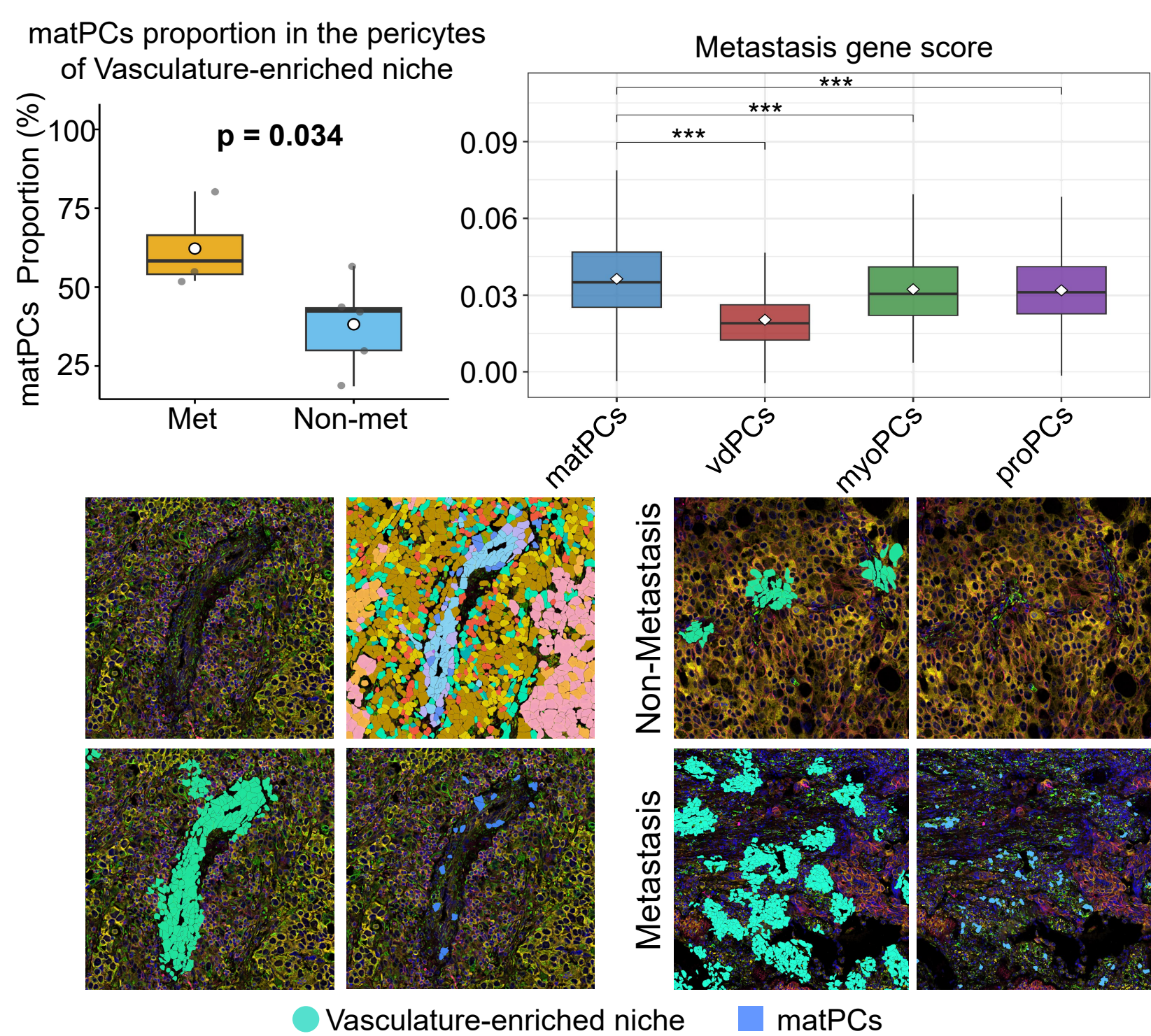
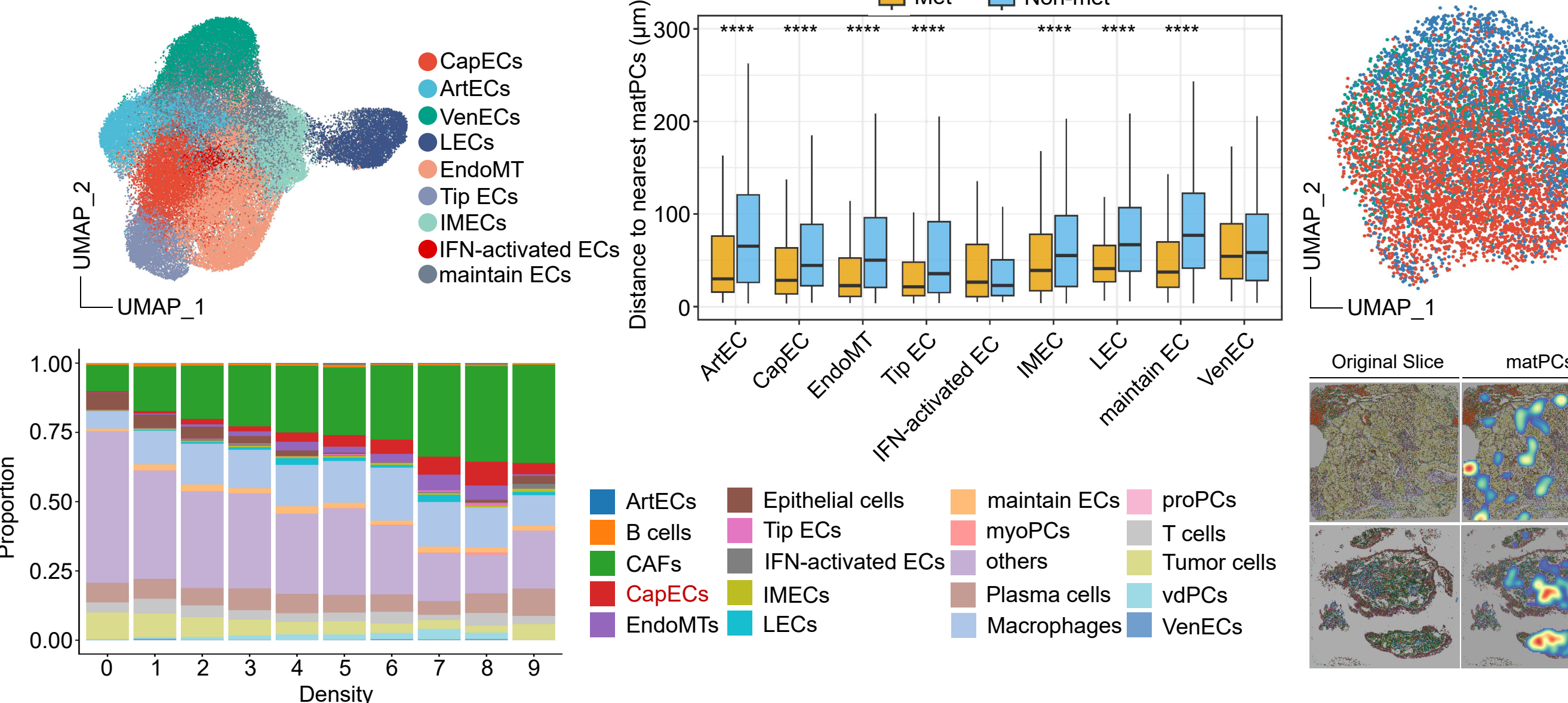


Figure2. Functional characterization identifies matPCs as a metastasis-associated pericyte state with enhanced extracellular matrix remodeling, cell–matrix adhesion, angiogenic activity, and adverse clinical relevance.



Functional Characterization Identifies matPCs as a Matrix-Remodeling and Pro-Metastatic Pericyte State

Functional enrichment analysis showed that matPCs were strongly associated with extracellular matrix organization, cell–matrix adhesion, and angiogenesis-related programs. Consistently, scMetabolism revealed enhanced glycosaminoglycan biosynthesis activity in matPCs, further supporting their matrix-remodeling phenotype. High matPC infiltration was significantly associated with poorer overall survival in TCGA-LUAD ($p = 0.043$). Pseudotime analysis placed matPCs predominantly at the terminal end of the pericyte differentiation trajectory, with tumor tissues showing a greater accumulation of matPCs at this terminal state. Notably, CytoTRACE indicated that matPCs retained relatively high developmental potential despite their terminal localization, suggesting a highly plastic pericyte state associated with metastatic progression.

Spatial Profiling Reveals Colocalization of matPCs with MMP14⁺ CapECs in Metastatic Tumors

Spatial analysis revealed that matPCs were positioned significantly closer to multiple endothelial cell subsets in metastatic NSCLC, with capillary endothelial cells (CapECs) showing the strongest association. The proportion of CapECs progressively increased with local matPC density, suggesting coordinated accumulation within metastatic vascular niches. Further subclustering identified an MMP14⁺ CapEC population that was enriched in metastatic tumors and exhibited marked spatial overlap with matPCs. The distance between matPCs and MMP14⁺ CapECs was significantly reduced in metastatic samples, and their local densities were positively correlated.

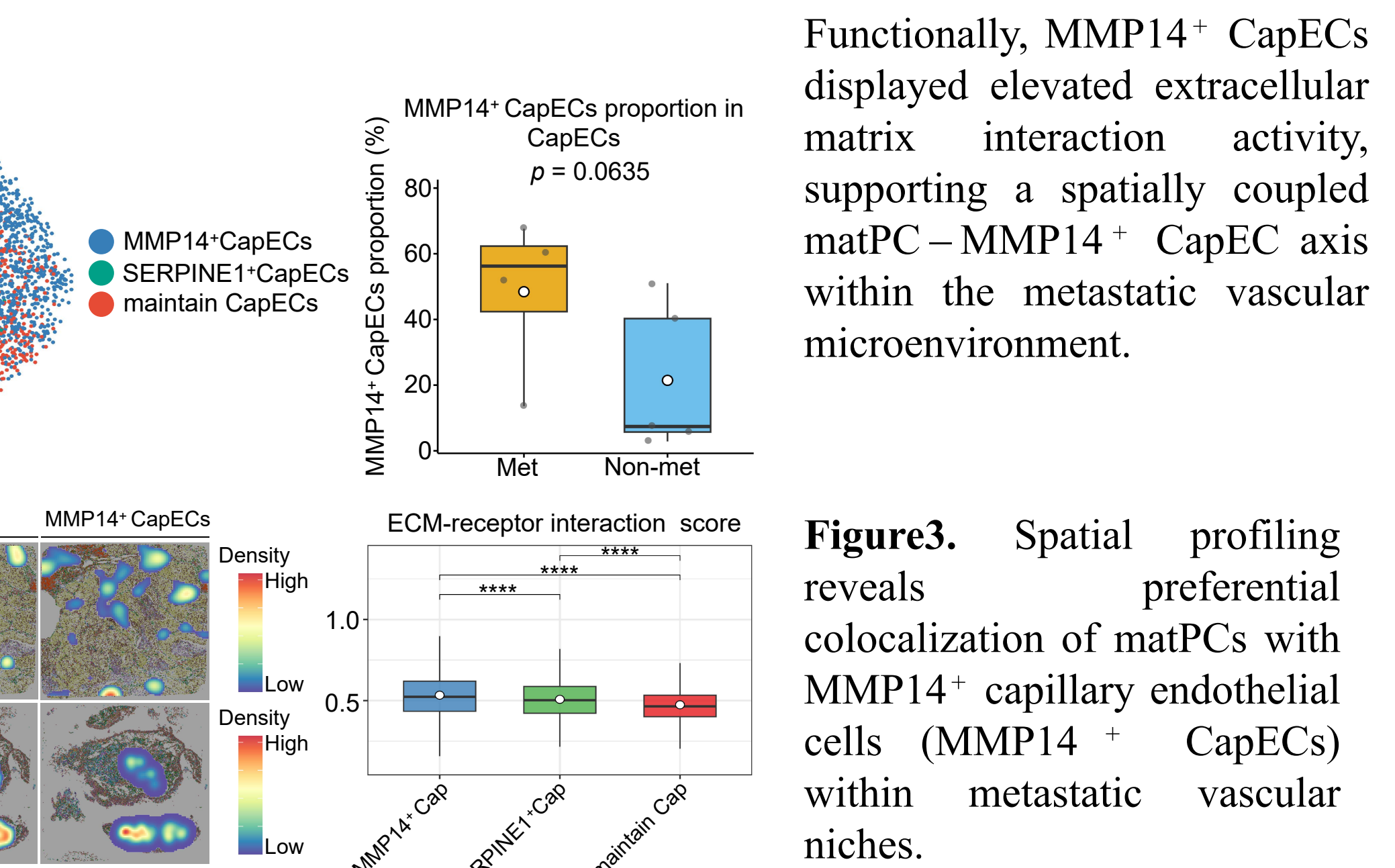


Figure3. Spatial profiling reveals preferential colocalization of matPCs with MMP14⁺ capillary endothelial cells (MMP14⁺ CapECs) within metastatic vascular niches.

Cell–Cell Communication Identifies CD44-Mediated Crosstalk Between matPCs and MMP14⁺ CapECs

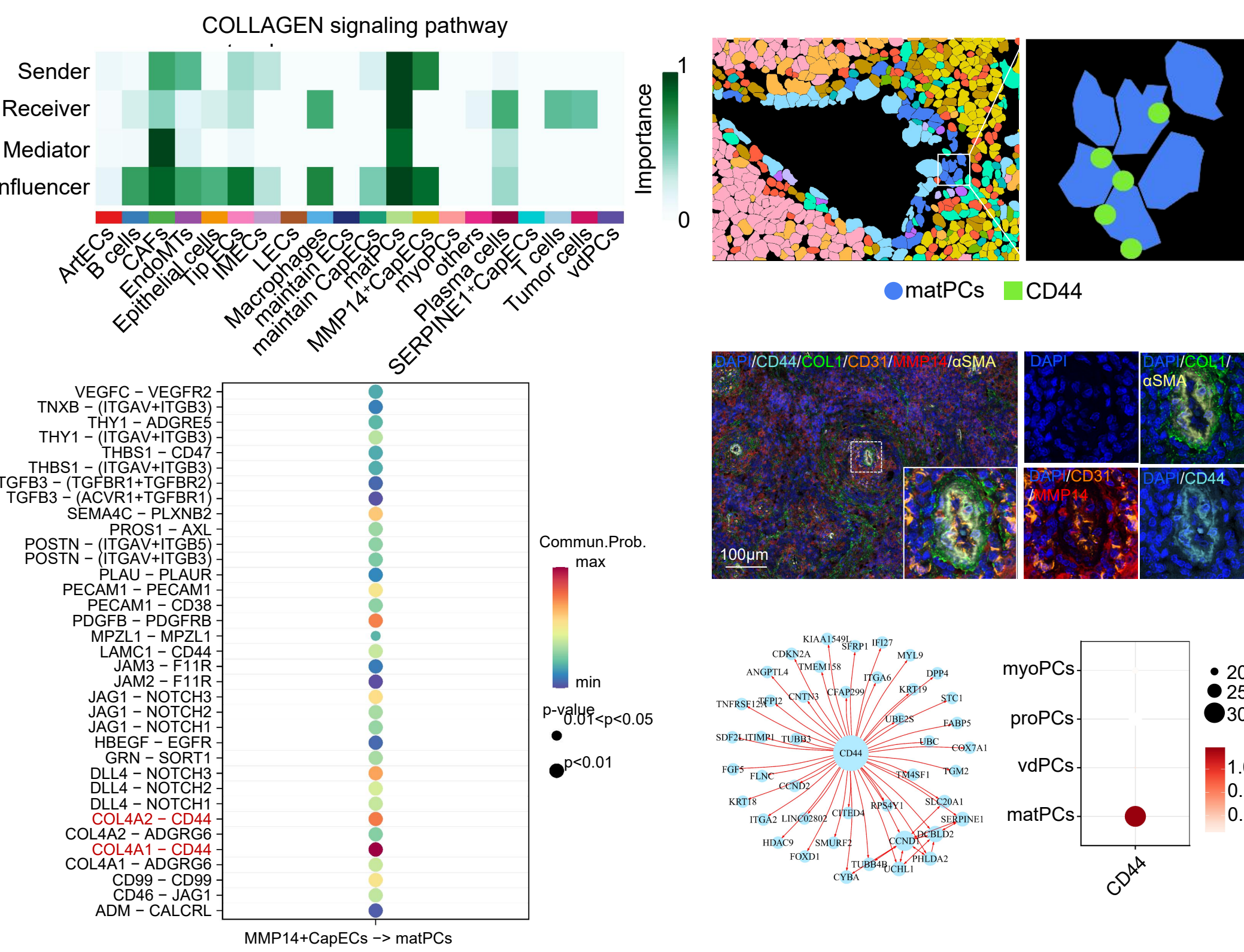


Figure4. Cell–cell communication analysis identifies robust crosstalk between matPCs and MMP14⁺ CapECs and highlights CD44 as a key regulator of the matrix-remodeling phenotype of matPCs.

Cell–cell communication analysis revealed robust signaling between matPCs and MMP14⁺ CapECs, with COLLAGEN signaling emerging as a dominant interaction pathway. Among the inferred ligand–receptor pairs, COL4A1/2–CD44 represented the strongest endothelial-to-pericyte communication axis. Spatial visualization and multiplex immunofluorescence further confirmed enrichment of CD44 in matPCs surrounding vascular structures. CD44 was preferentially expressed in matPCs compared with other pericyte subsets and showed extensive connectivity with extracellular matrix remodeling-associated genes, highlighting CD44 as a key regulatory hub mediating the matrix-remodeling phenotype of matPCs.

DISCUSSION

Discussion

Our findings expand the conventional view of pericytes as passive vascular-supporting cells and identify matPCs as an active component of the metastatic vascular microenvironment in NSCLC. Their preferential localization within vascular niches, together with enhanced extracellular matrix remodeling and angiogenic programs, suggests that matPCs may facilitate metastatic dissemination by reshaping the perivascular microenvironment. Importantly, the close spatial and molecular coupling between matPCs and MMP14⁺ CapECs highlights a coordinated stromal–vascular interaction that may further promote metastatic progression. COL4A1/2–CD44 signaling emerged as a potential regulatory axis linking endothelial cues to the matrix-remodeling phenotype of matPCs. These findings provide a spatially resolved framework for understanding pericyte–endothelial cooperation in NSCLC metastasis and suggest that targeting the matPC-associated vascular niche may represent a potential strategy for metastasis-directed therapy.

Abbreviations

NSCLC, non-small cell lung cancer; PC, pericyte; matPC, matrix-remodeling pericyte; CapEC, capillary endothelial cell; MMP14, matrix metalloproteinase 14; ECM, extracellular matrix; scRNA-seq, single-cell RNA sequencing; ST, spatial transcriptomics