Integrin α5β1-mediated multicellular crosstalk in the tumor microenvironment drives bladder cancer progression and reveals targetable vulnerabilities

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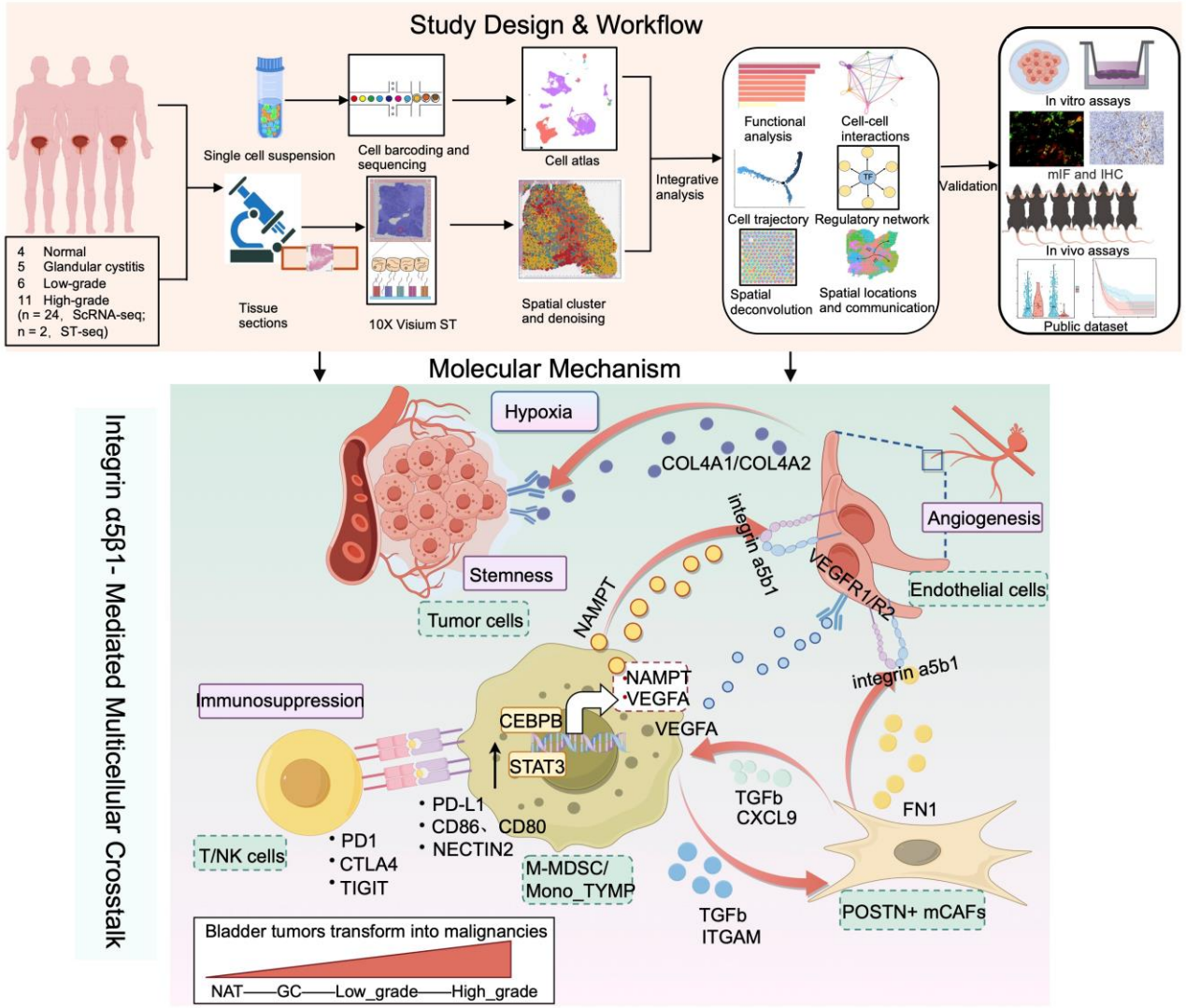
Introduction

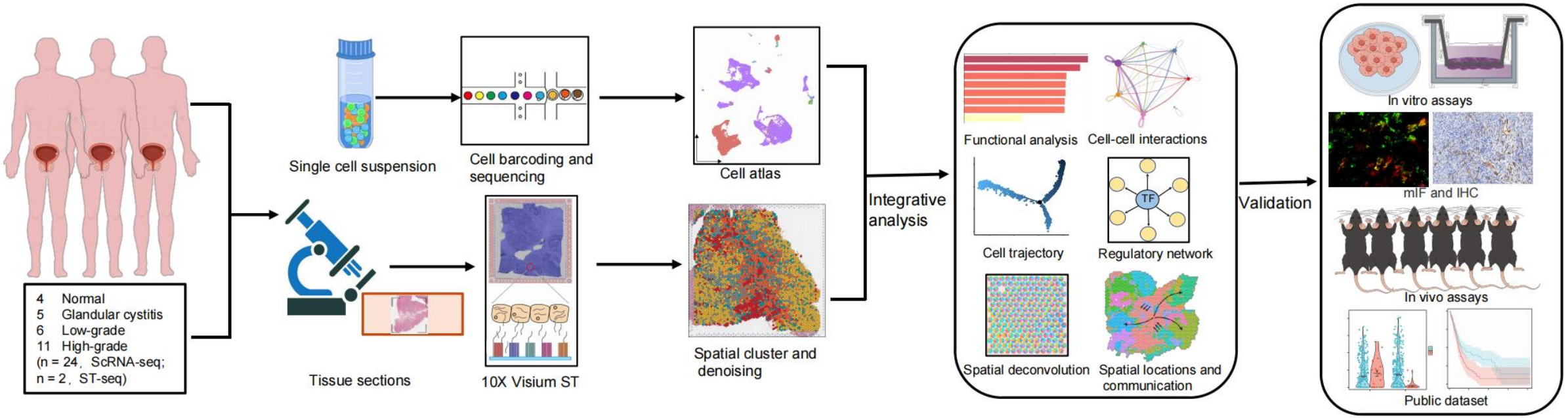
Bladder cancer (BCa) progression is driven by complex interactions within the tumor microenvironment; however, the multicellular communication networks underlying this process remain incompletely characterized.



- This study integrates single-cell and spatial multi-omics to elucidate an integrin α5β1-mediated multicellular communication network (mCAFs/MDSCs–endothelial cells–tumor cells) in the bladder cancer microenvironment that drives angiogenesis and tumor stemness, and further develops a drug-loaded hydrogel system targeting this pathway to synergistically enhance immunotherapeutic efficacy.

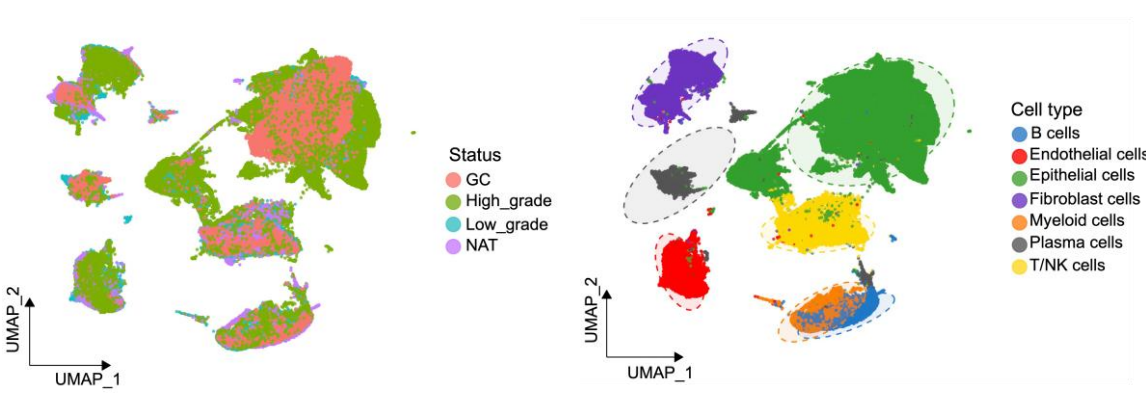
Highlights

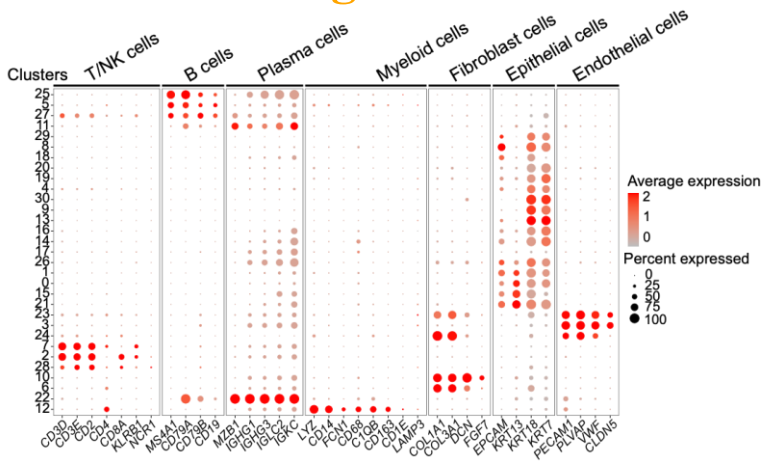
- SDC1+ epithelial cells, POSTN+ mCAFs, and M-MDSCs are enriched in high-grade bladder cancer.
- Co-localized mCAF-FN1 and M-MDSC-NAMPT engage integrin α5β1 to drive angiogenesis.
- Tip endothelial cells then reinforce tumor stemness via COL4A1/2–SDC1 signaling.
- Targeting the integrin α5β1 cascade enhances immune checkpoint blockade efficacy.

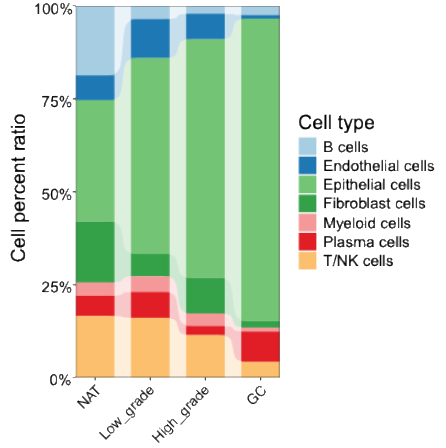


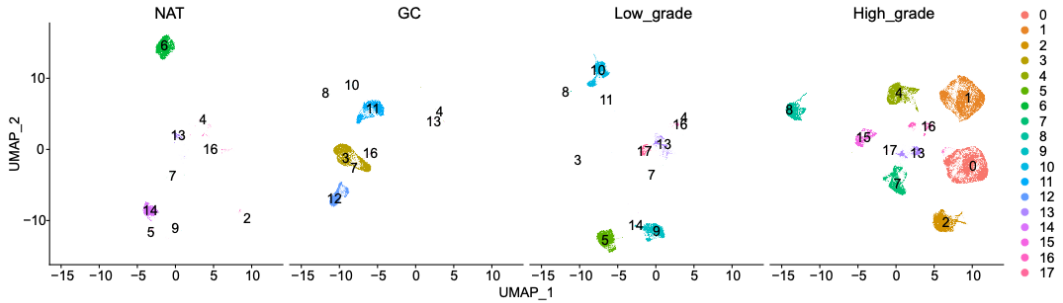
Results

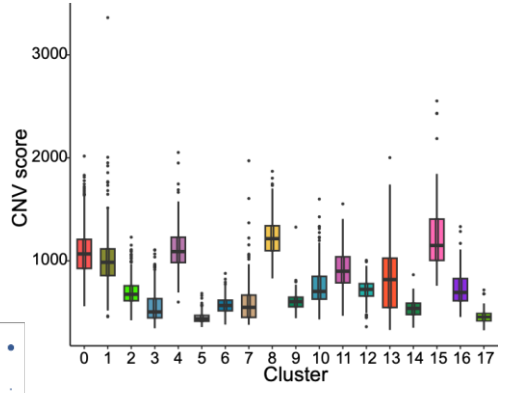
Identification of a distinct epithelial cell cluster linked to malignant transformation phenotypes

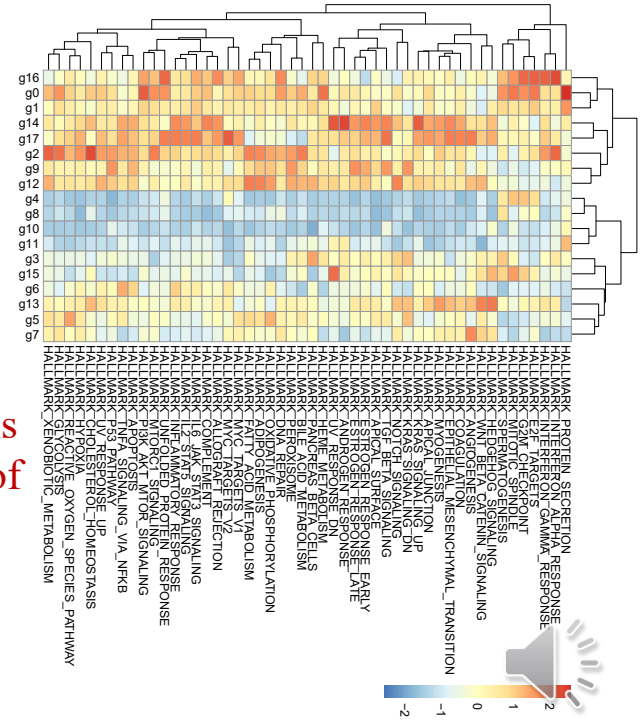


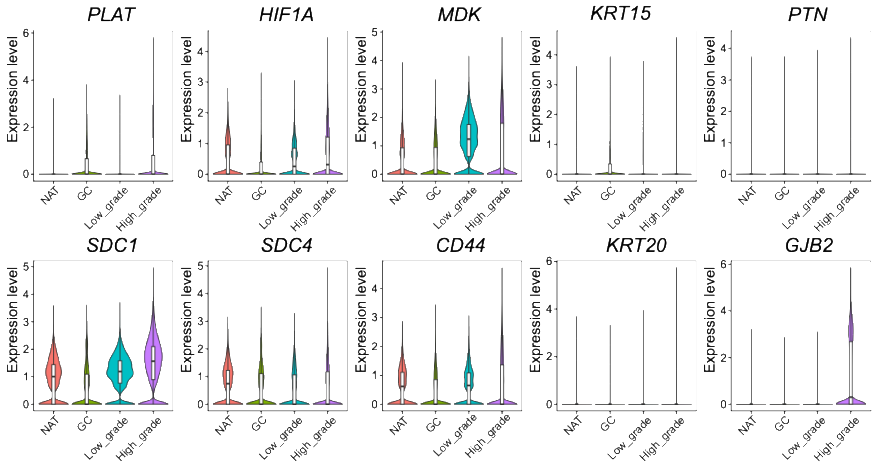


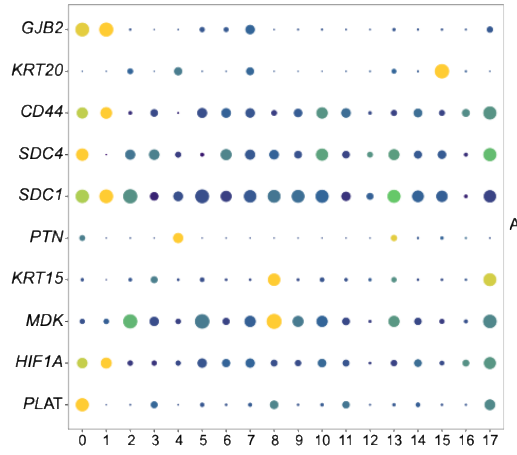






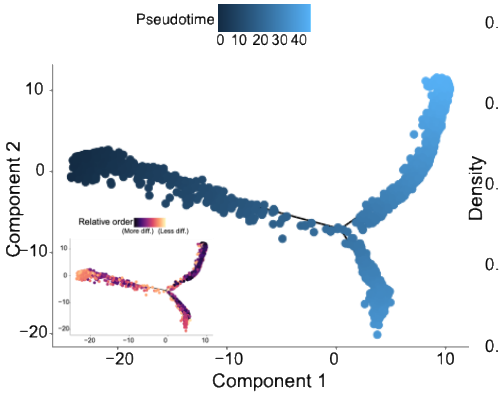


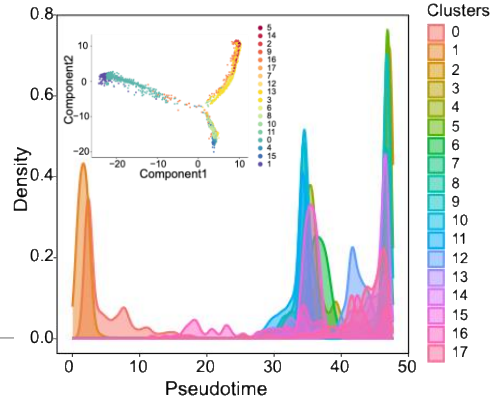


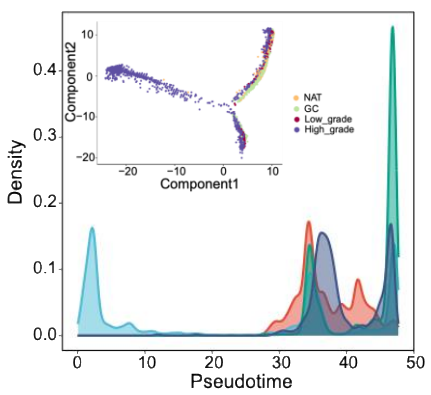


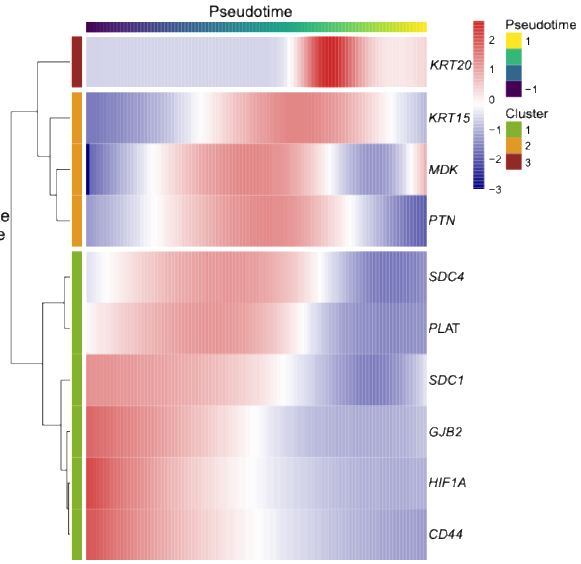
- Single-cell sequencing reveals the cellular atlas of malignant progression in bladder cancer.

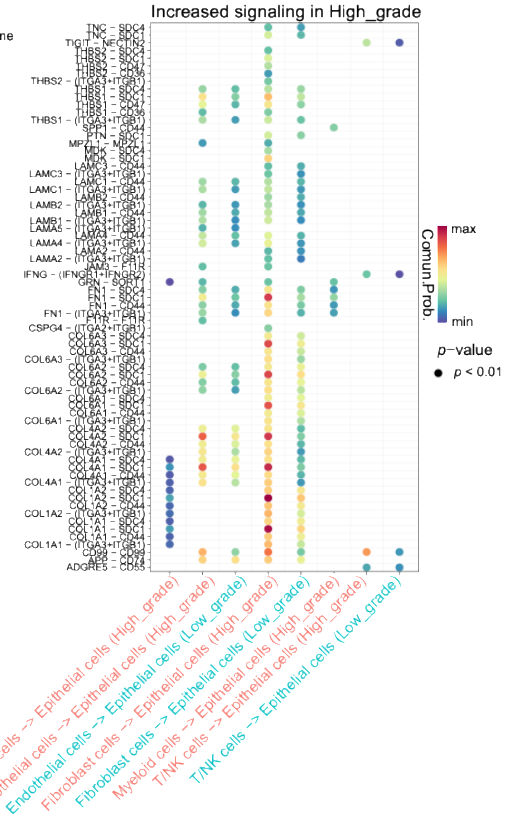
Results

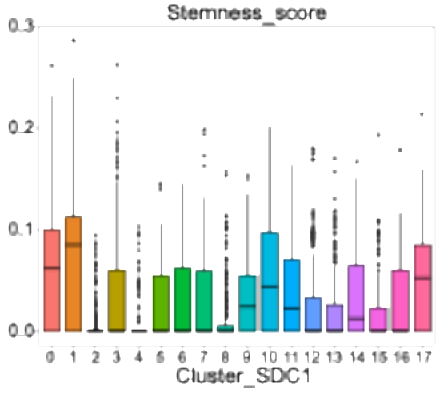


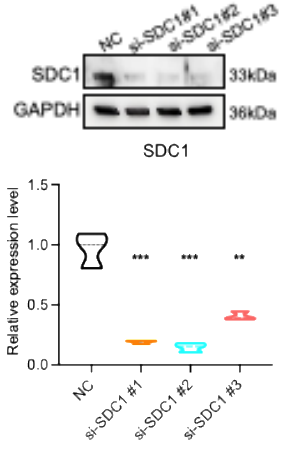


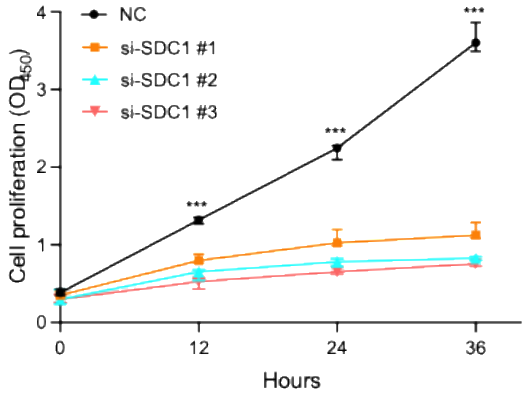


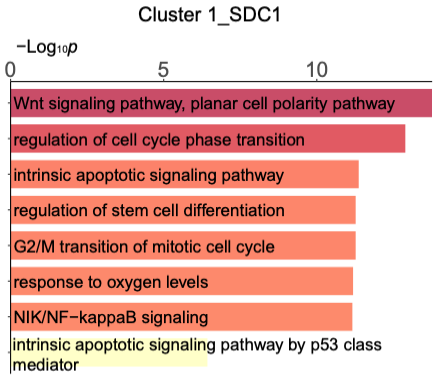


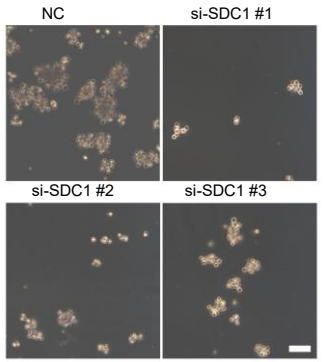


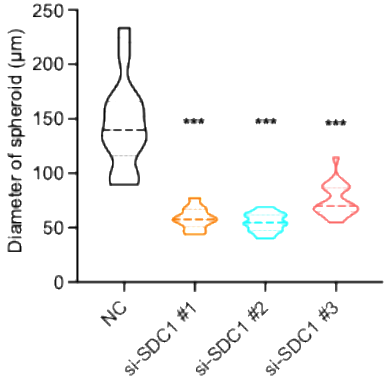








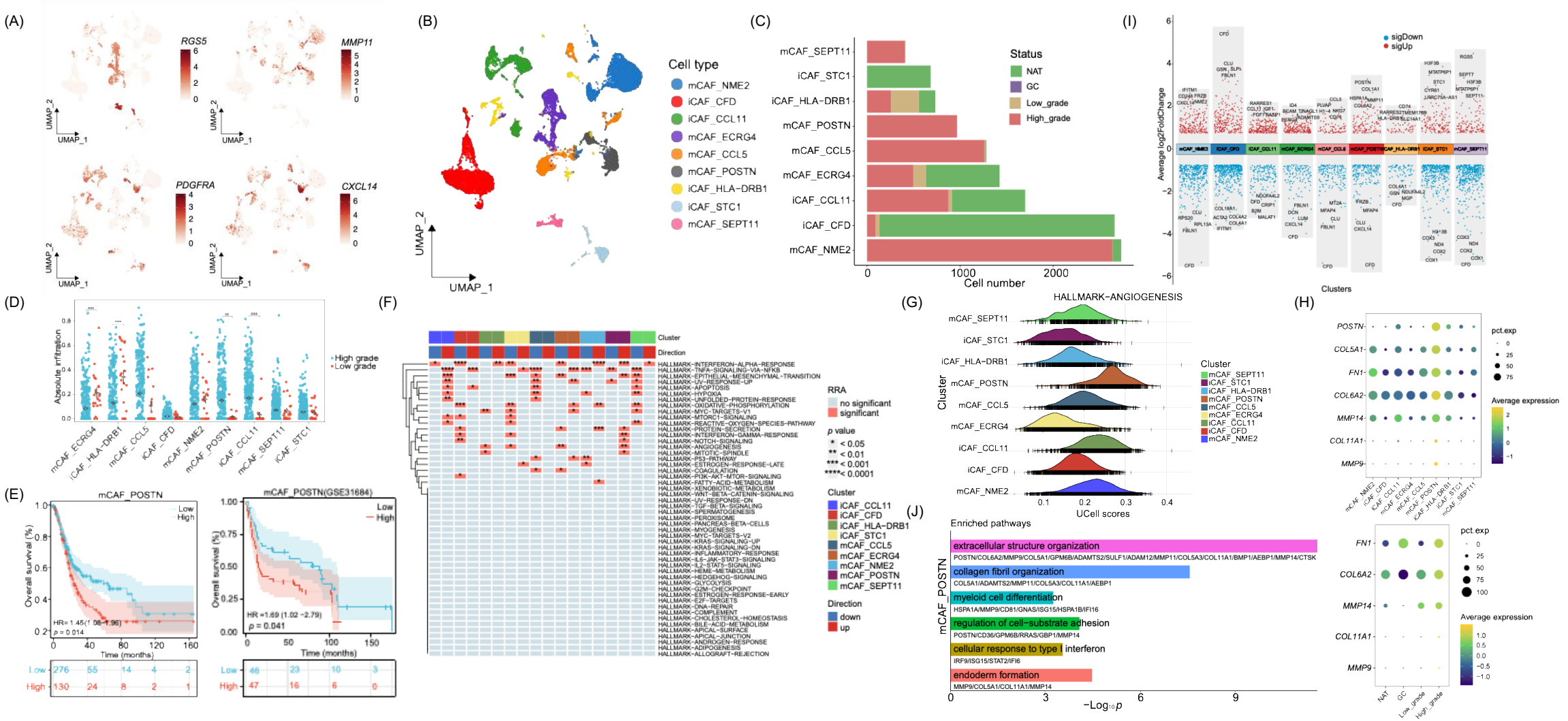




- Notably, a stem-like epithelial subpopulation with high SDC1 expression (Cluster 1_SDC1) is positioned at the root of this evolutionary trajectory. This population not only directly drives tumor proliferation and migration, but also remodels the tumor microenvironment through collagen-mediated signaling.

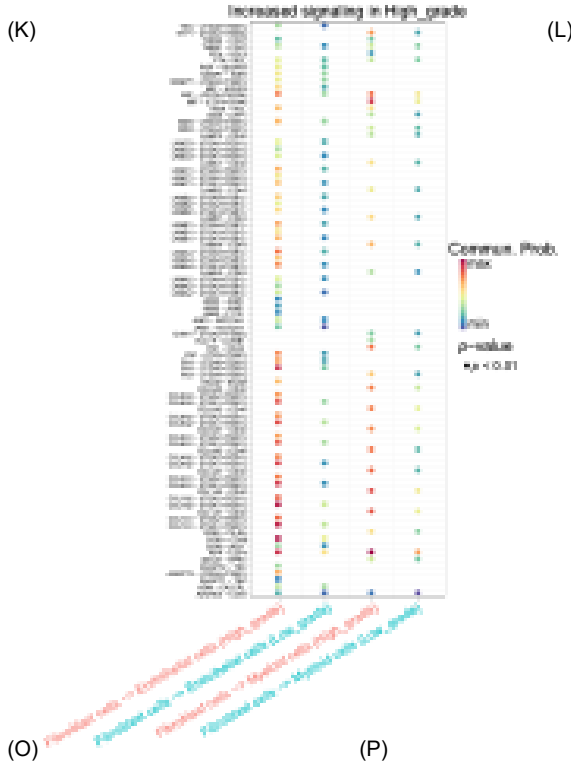
Results

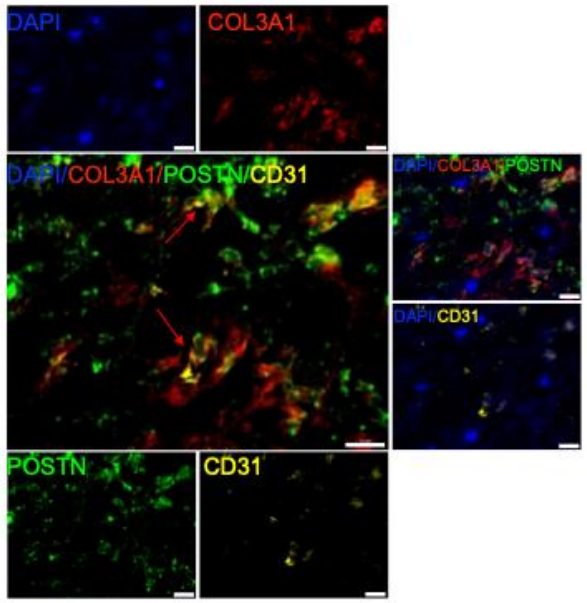
Prognostic implications of POSTN+ mCAFs in high-grade BCa

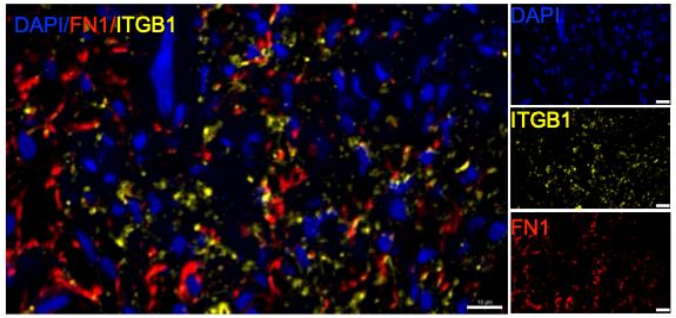


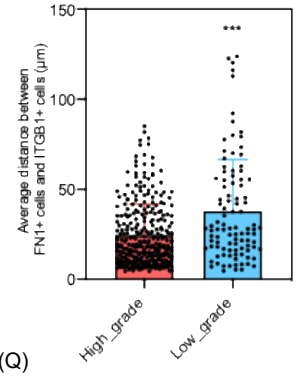
- POSTN+ myofibroblastic CAFs (mCAFs) are specifically enriched in high-grade bladder cancer and are strongly associated with poor patient survival outcomes.

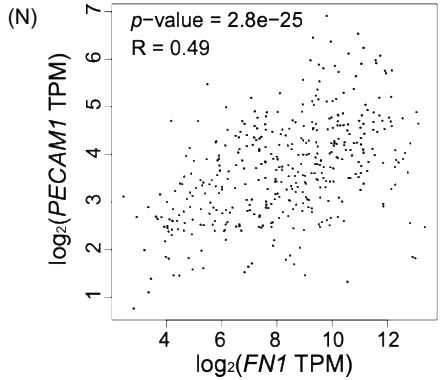
Results

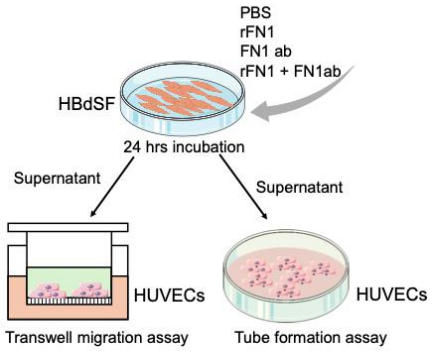


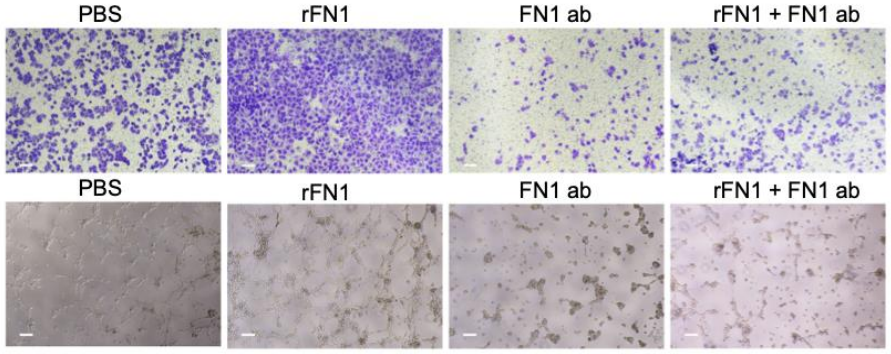


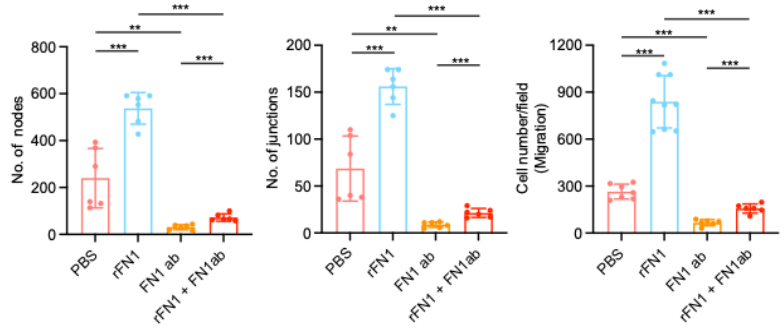








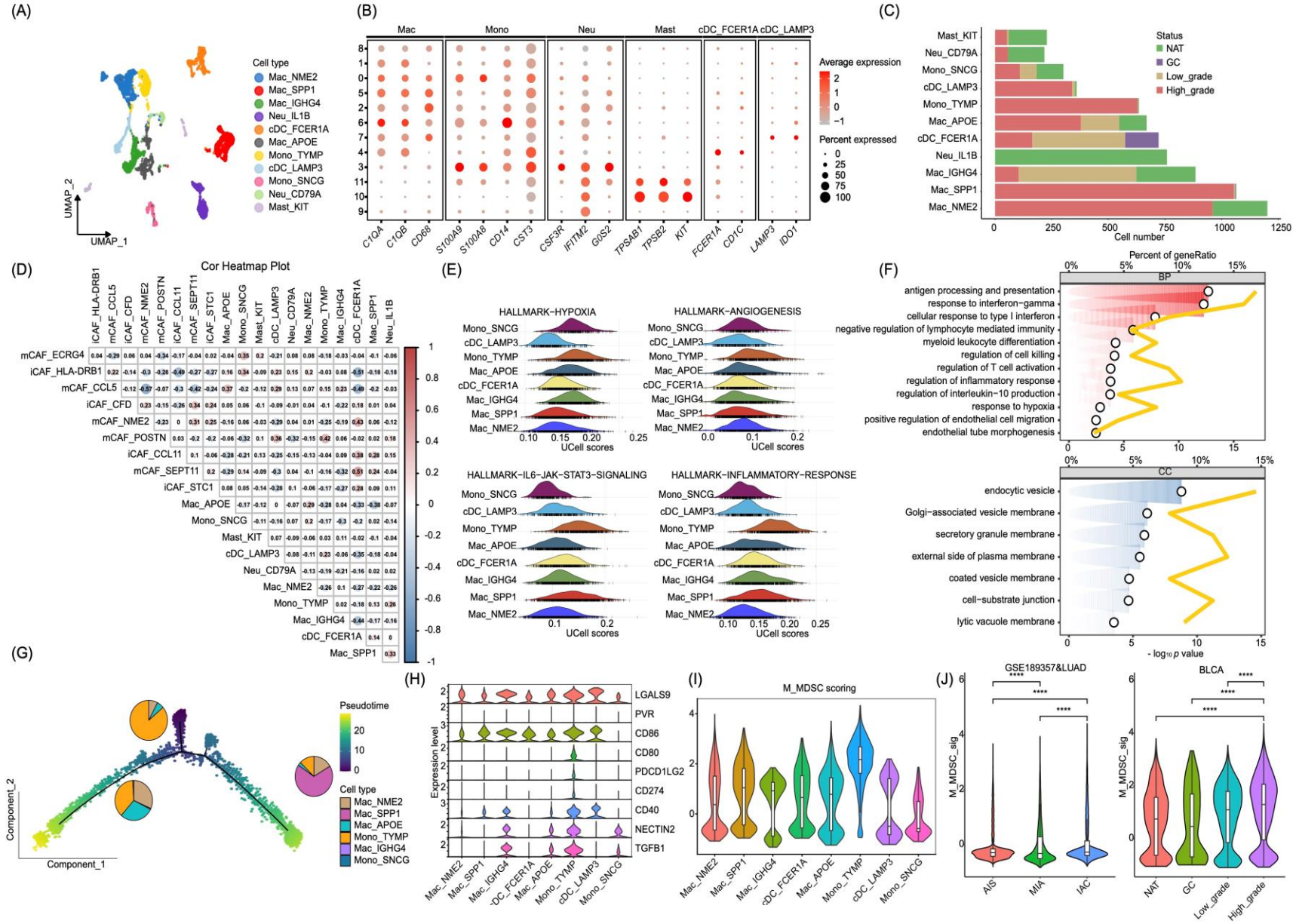




- This subpopulation promotes tumor angiogenesis by secreting FN1, which selectively binds to integrin α5β1 on endothelial cells, thereby directly driving the formation of a neovascular network.

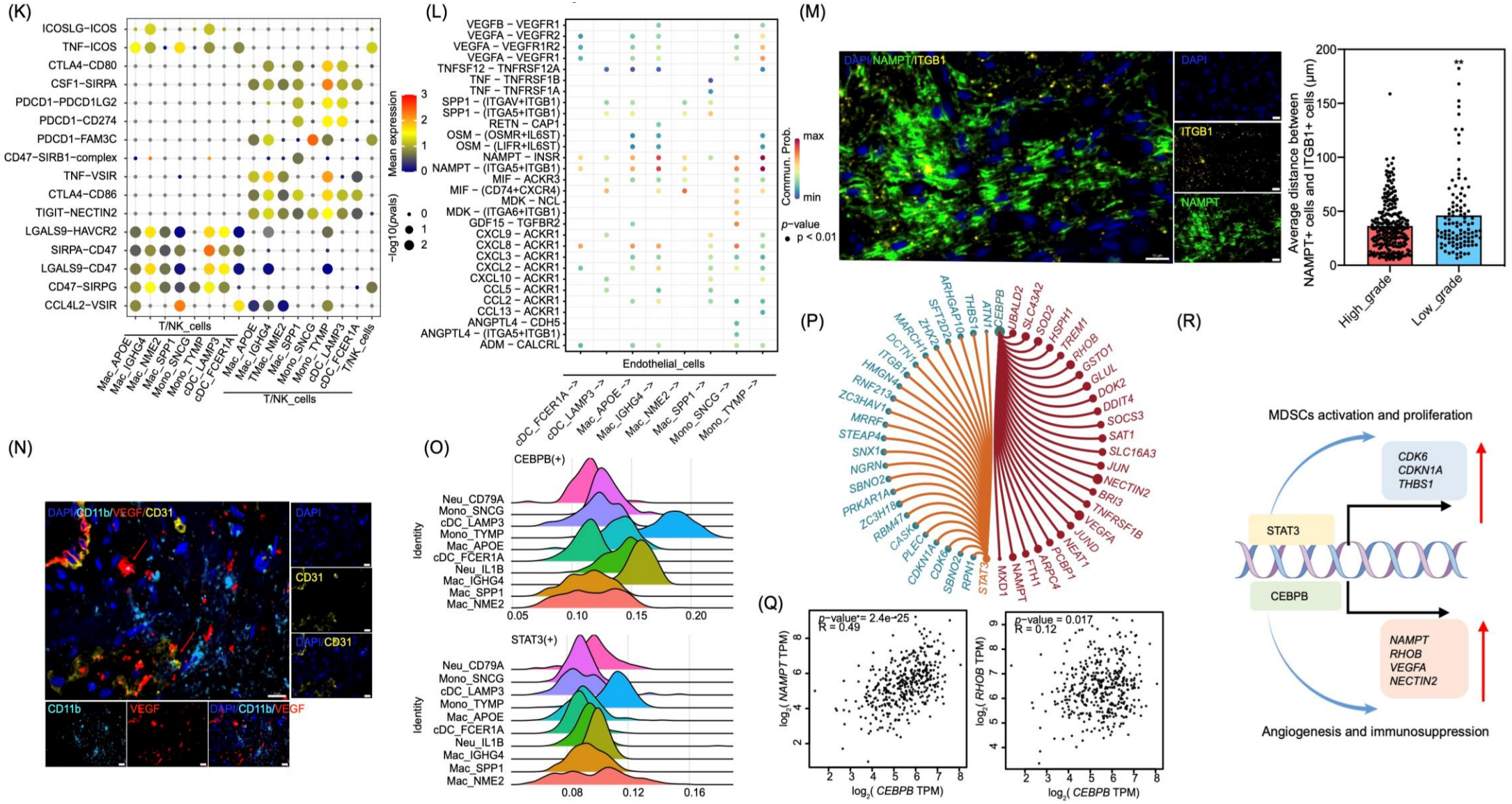
Results

Preferential enrichment of MDSCs and their contribution to immune suppression and angiogenesis in high-grade BCa



- In high-grade tumors, a TYMP-high monocytic MDSC subpopulation was identified, which shows progressive enrichment during tumor evolution and exhibits a pronounced immunosuppressive transcriptional program.

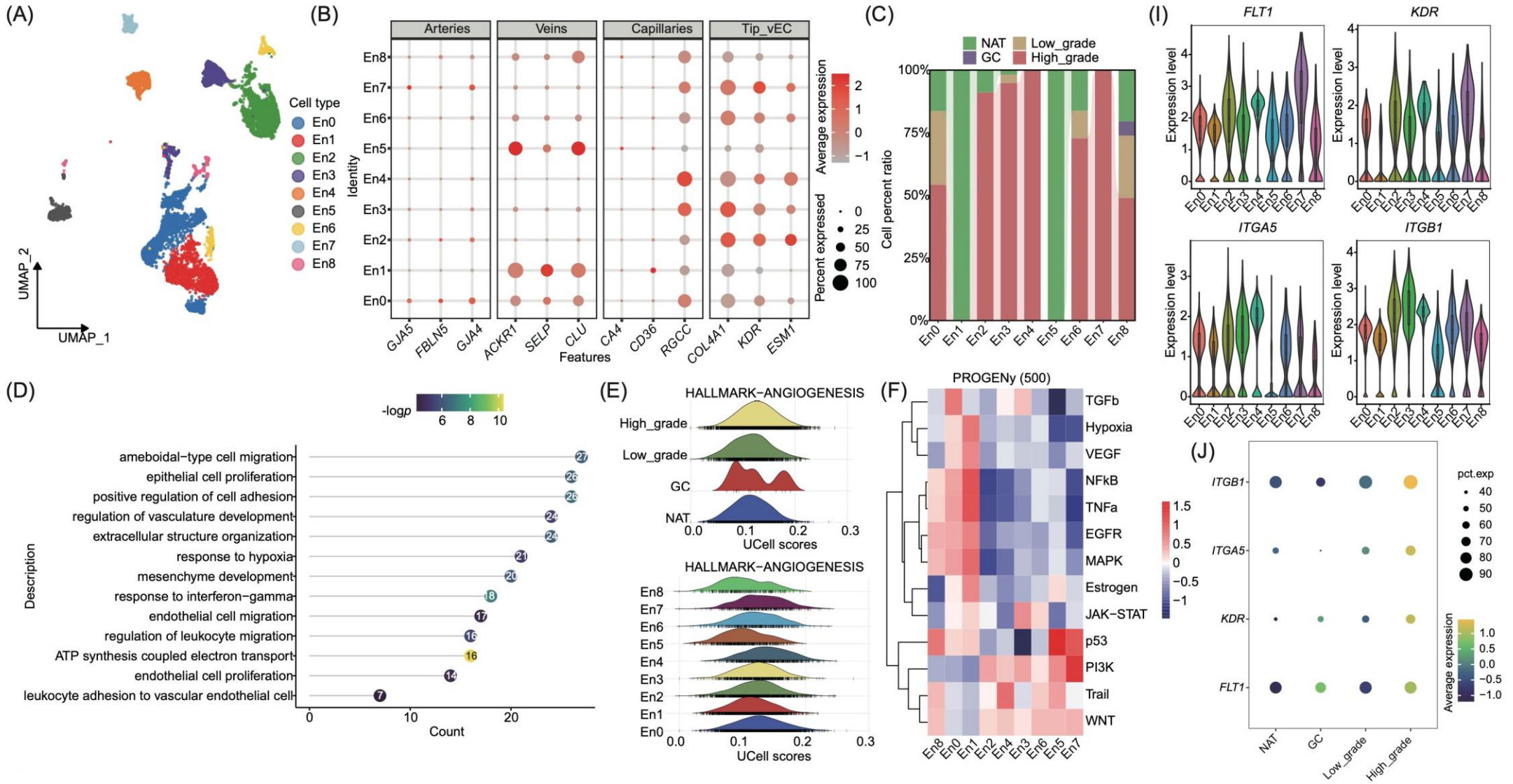
Results



- This subset is driven by a core STAT3/CEBPB regulatory network. It suppresses T and NK cell activity through co-inhibitory ligands such as CD274, and concurrently targets endothelial cells via the NAMPT/VEGFA axis, thereby synergistically promoting tumor angiogenesis.

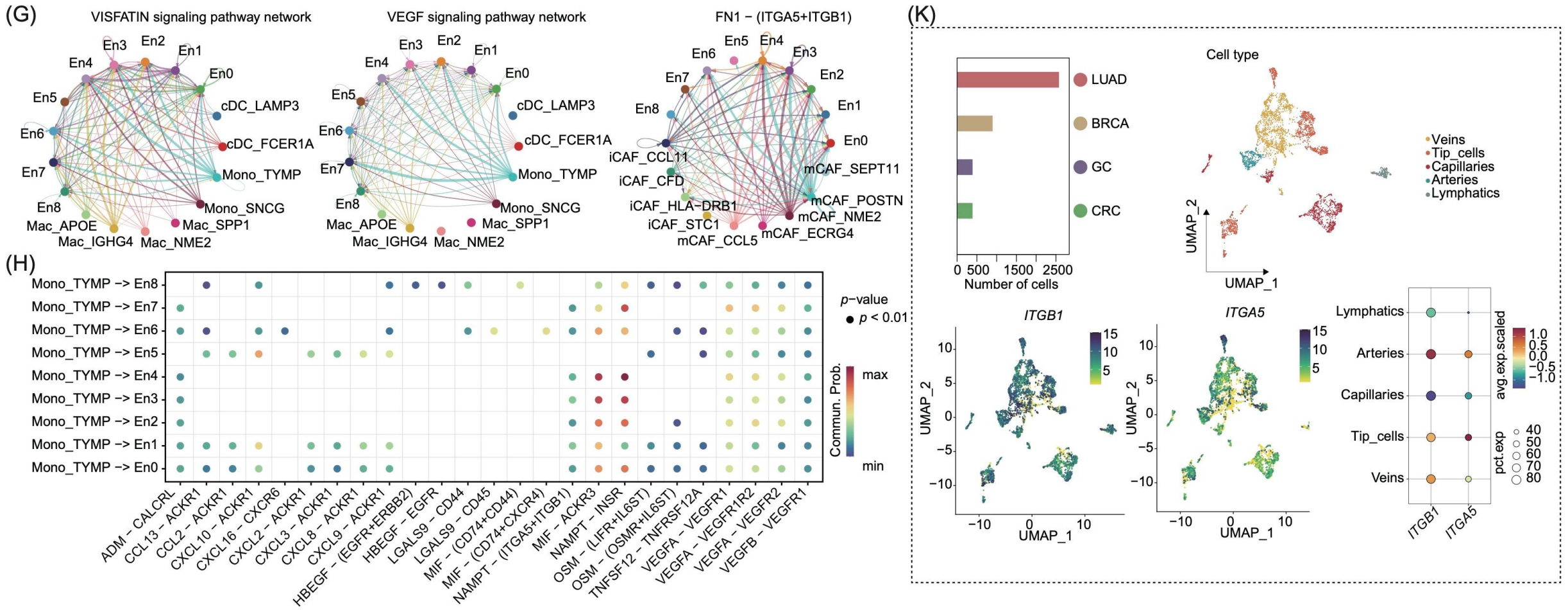
Results

Crosstalk between tip_vECs and POSTN+ mCAFs/MDSCs through integrin α5β1 fosters angiogenesis



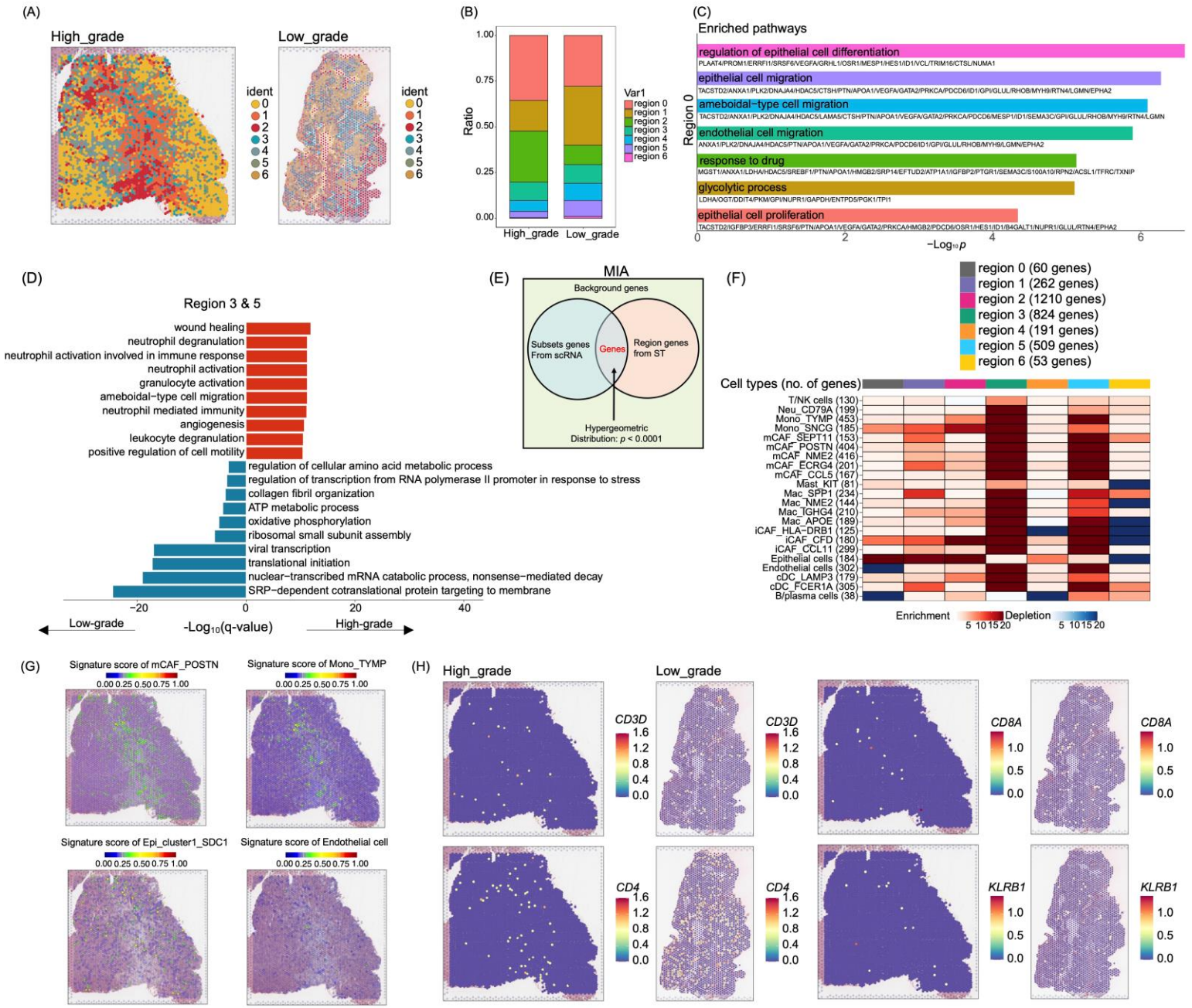
- In high-grade tumors, a tip endothelial cell population characterized is specifically enriched, with activation of key pro-angiogenic pathways, including PI3K and COX2.

Results



- Mechanistically, mCAFs and MDSCs cooperatively activate integrin α5β1 on Tip_vECs through secretion of FN1 and NAMPT, respectively. This stroma–vascular pro-angiogenic mechanism is highly conserved across cancer.

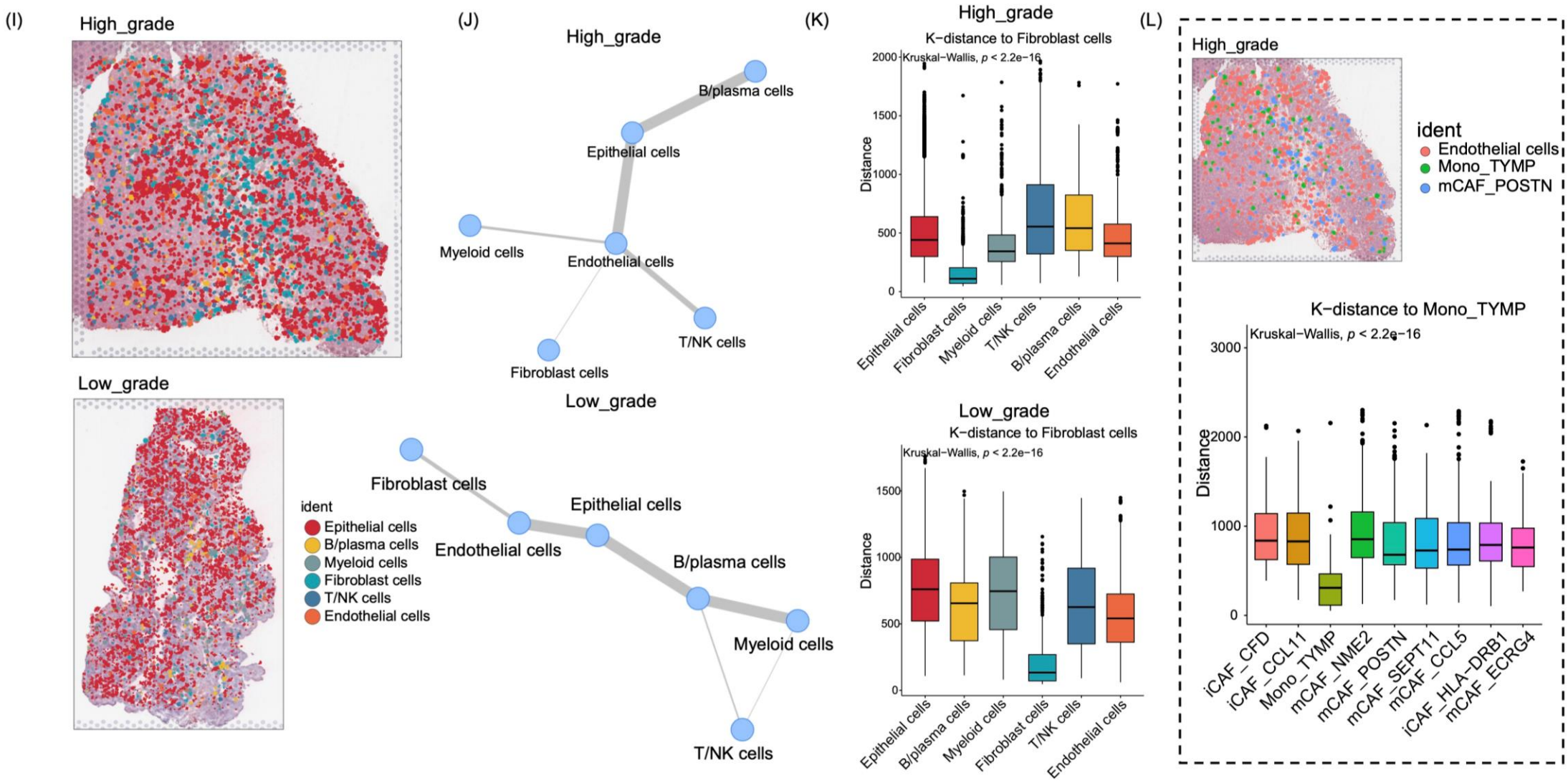
Results



Spatial architecture and multicellular signaling cascades in high-grade BCa

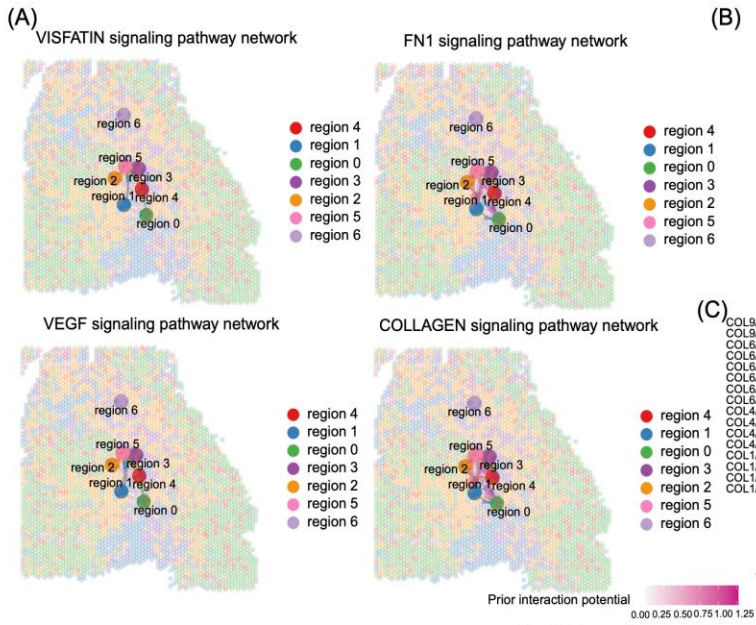
- High-grade bladder cancer exhibits a clear compartmentalization between tumor and stromal regions.
- T/NK cell infiltration is limited within the tumor compartment. In contrast, the stromal compartment is enriched with POSTN+ mCAFs, TYMP-high monocytic cells, and endothelial cells, along with relatively higher T/NK cell presence.

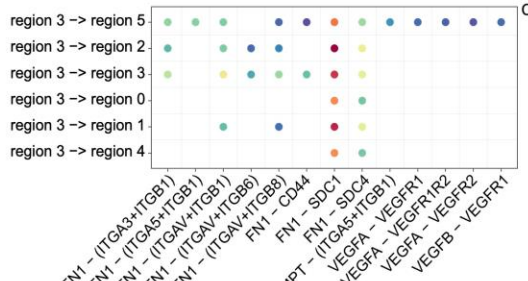
Results

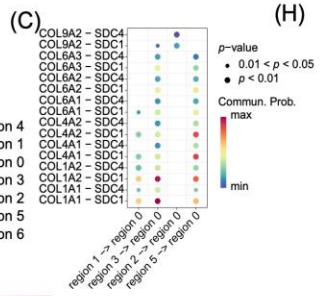


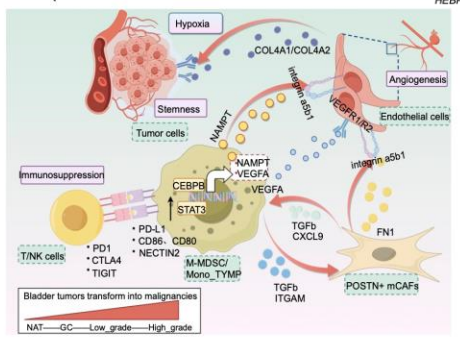
- POSTN+ mCAFs are in closest spatial proximity to TYMP-high monocytes.

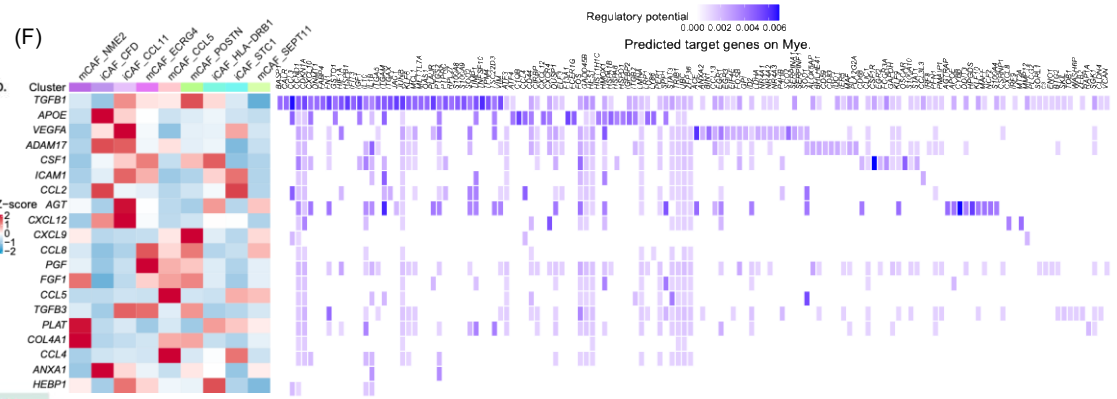
Results

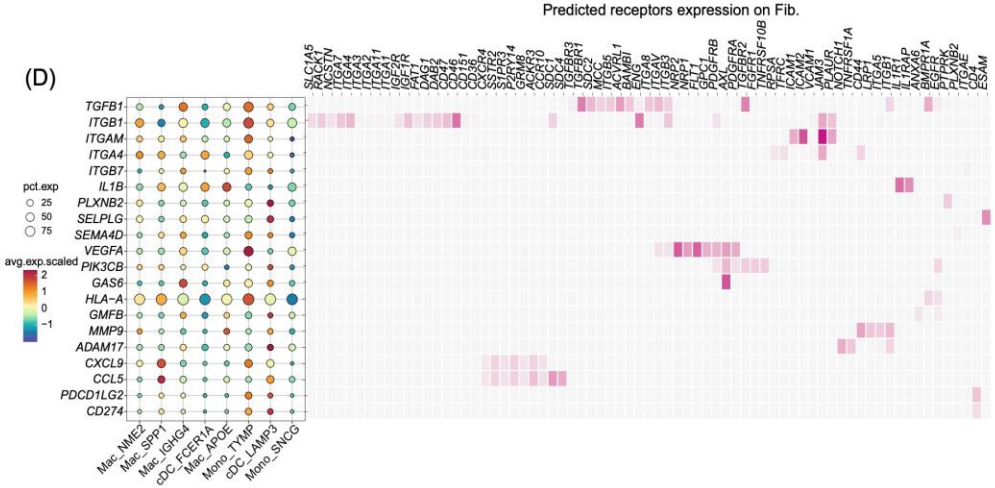


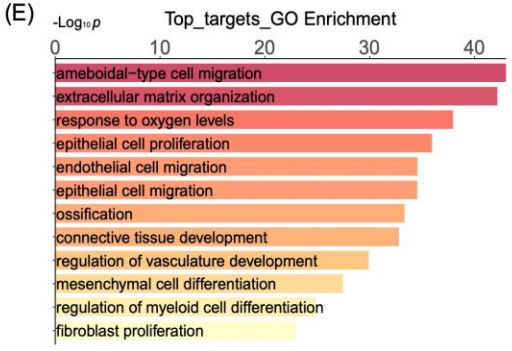


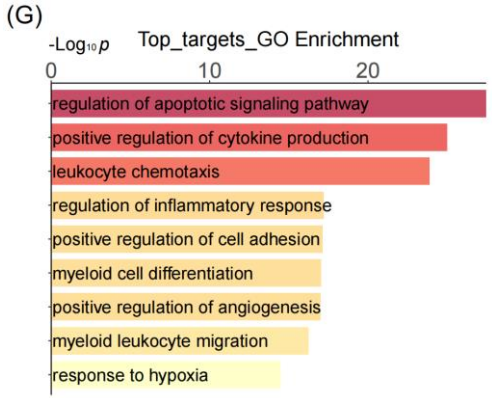








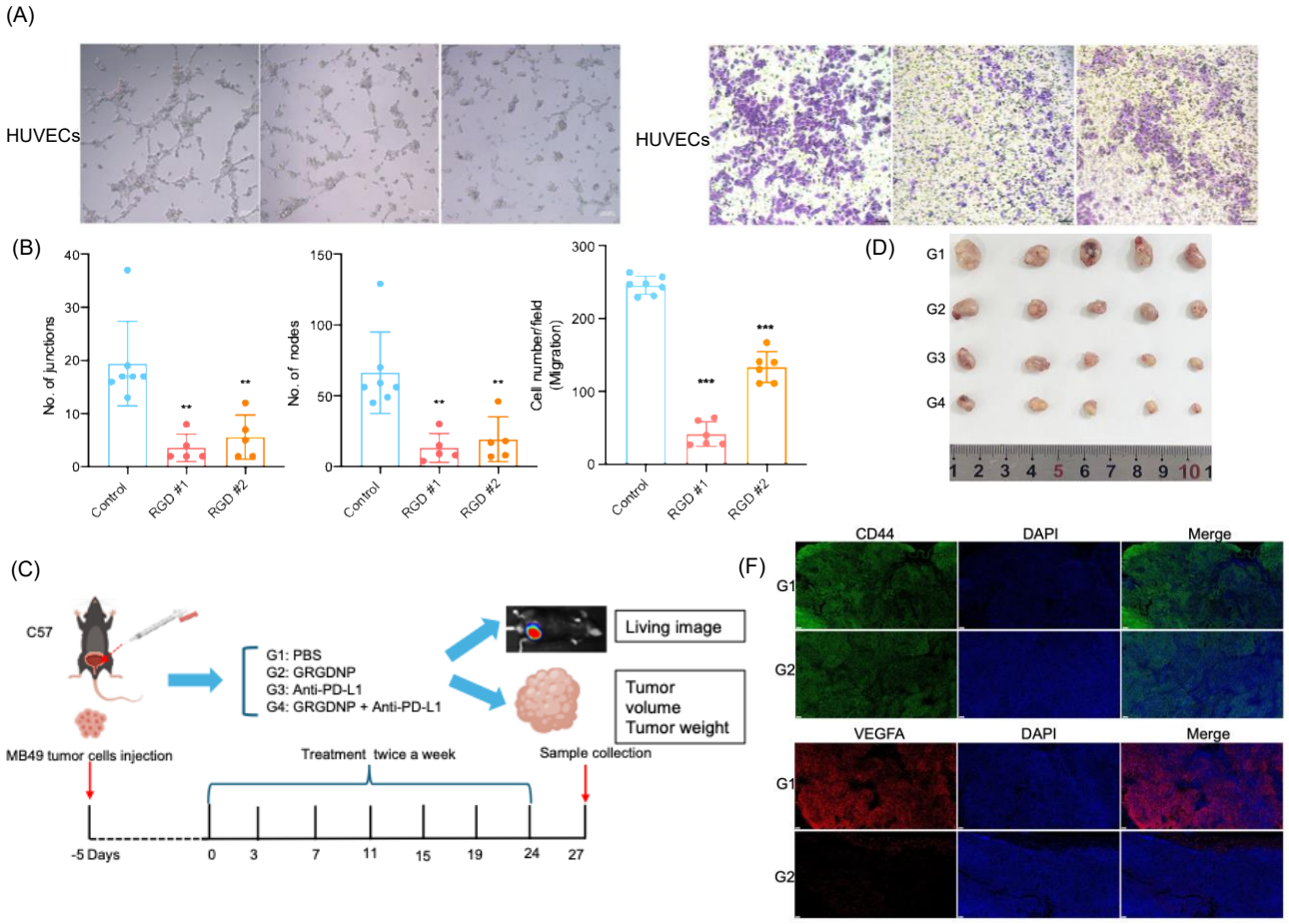


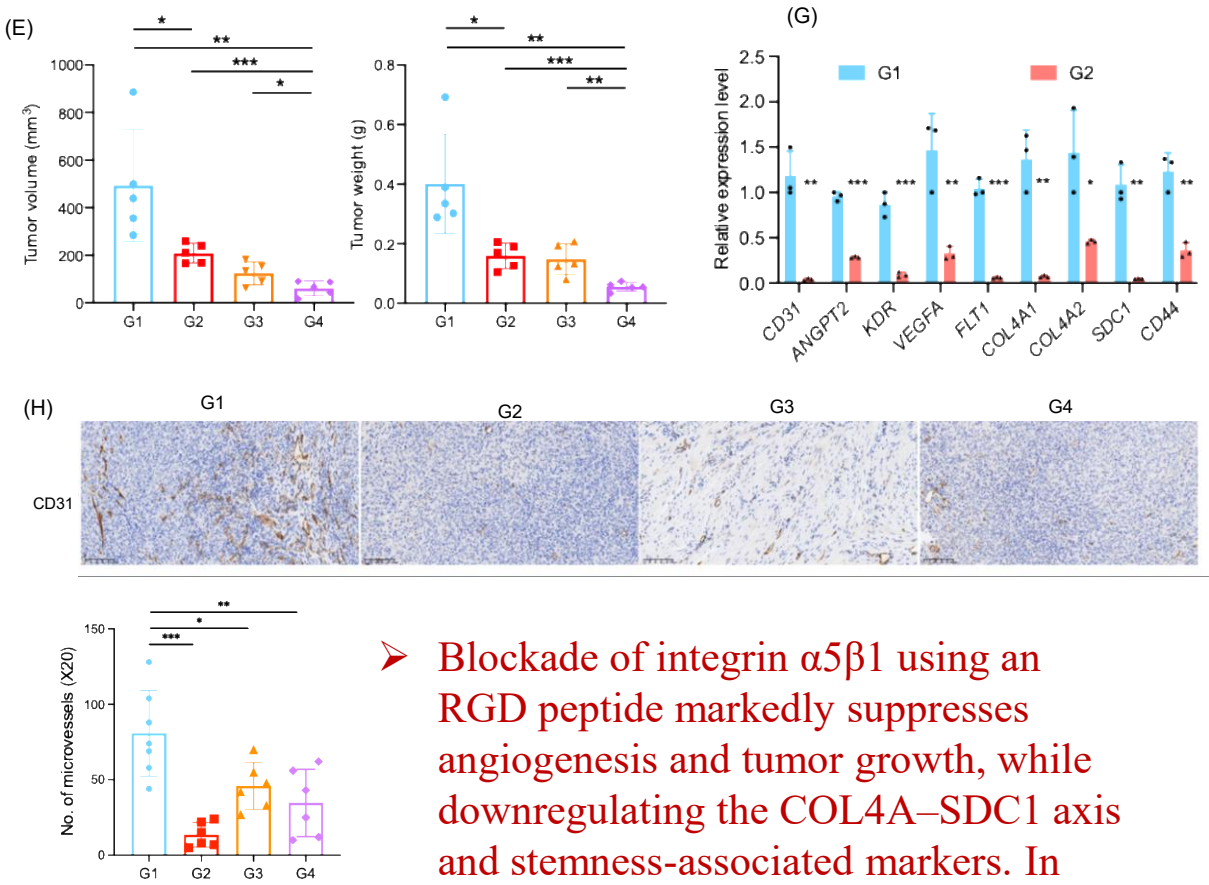


- POSTN+ mCAFs and TYMP-high monocytes engage in bidirectional signaling crosstalk, coordinately regulating ECM remodeling, angiogenesis, and myeloid cell function.

Results

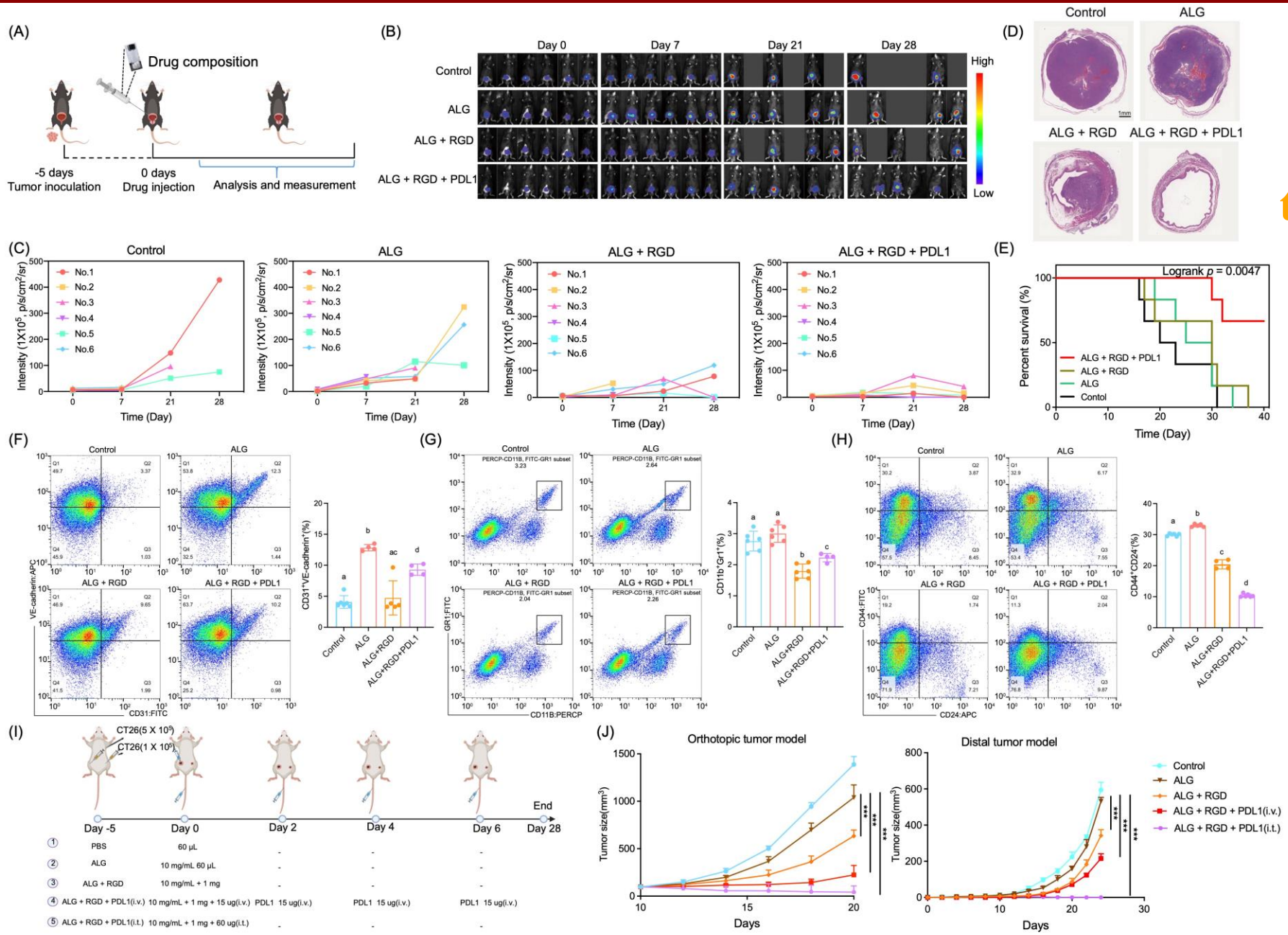
Therapeutic targeting of integrin α5β1 potentiates immunotherapy in BCa models





- Blockade of integrin α5β1 using an RGD peptide markedly suppresses angiogenesis and tumor growth, while downregulating the COL4A–SDC1 axis and stemness-associated markers. In combination with anti–PD-L1 therapy, it further enhances antitumor efficacy.

Results



RGD peptide hydrogel system enhances broad anti-tumor immunotherapy efficacy

- Local delivery of an RGD peptide hydrogel suppresses angiogenesis, immunosuppression, and tumor stemness, resulting in marked inhibition of tumor growth.
- Combination with anti–PD-L1 therapy further enhances efficacy, with intratumoral delivery outperforming systemic administration.

Summary

- Integrative multi-omics analyses reveal that POSTN+ mCAFs and TYMP-high monocytes cooperatively establish an immunosuppressive and pro-angiogenic microenvironment in high-grade bladder cancer;
- FN1 and NAMPT derived from mCAFs and MDSCs drive angiogenesis via integrin α5β1 and sustain tumor stemness through the COL4A1/2–SDC1 axis;
- Targeting integrin α5β1 enhances the efficacy of immunotherapy, and hydrogel-based delivery further improves therapeutic outcomes, indicating broad-spectrum antitumor potential.

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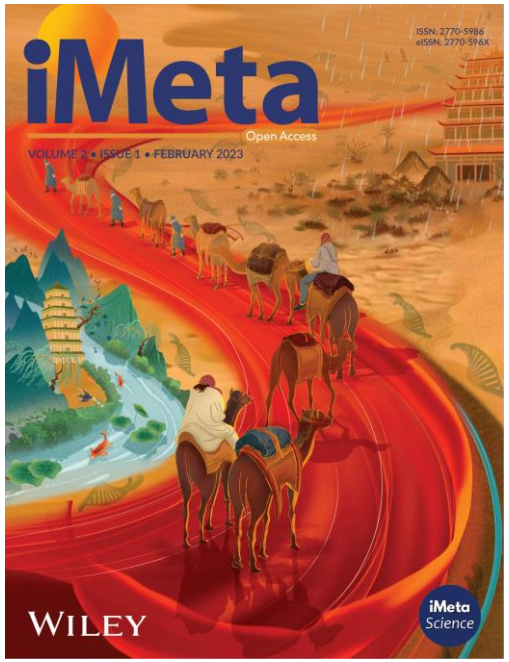

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