



P2.136: MEOX1-Driven Maturation of TU-HEVs Sensitizes Tumors to Anti-Angiogenic and Immune Combination Therapy

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INTRODUCTION

- Combining anti-angiogenic and immunotherapy is a key strategy for advanced NSCLC, but patient selection criteria and synergistic mechanisms remain unclear^[1].
- Tumor-associated high endothelial microveins (TU-HEVs) drive immune cell infiltration and tertiary lymphoid structure formation, with their density positively correlating with treatment efficacy^[2,3].
- The regulatory mechanisms governing TU-HEVs during this combination therapy remain to be elucidated.

METHODS

Design:

- Integrated single-cell and spatial transcriptomics from 19,923 endothelial cells across 17 cancers to identify lymphocyte-associated post-capillary venule (PCV) subpopulations.
- Validated via ChIP-seq, CUT&Tag, and Dual-Luciferase reporter assays that candidate transcription factor MEOX1 directly regulates CHST2, an enzyme essential for TU-HEV maturation.
- Demonstrated in an orthotopic murine lung cancer model that endothelial-targeted delivery of MEOX1 (AAV2/9-TIE-MEOX1) drives TU-HEV formation and enhances CD8⁺T-cell infiltration.

DISCUSSION AND CONCLUSION

Actionable Take Away Message

- The MEOX1–CHST2 axis drives TU-HEV maturation to enhance CD8⁺T-cell infiltration and remodel immunosuppressive microenvironments.
- Endothelial MEOX1 delivery overcomes combination therapy resistance, and its signature predicts superior ORR and OS in NSCLC.

Future Direction for Research

- Develop clinical delivery systems to pharmacologically induce in situ TU-HEVs
- Validate MEOX1/MECA79 in prospective trials to refine patient selection and explore synergistic combinations.

REFERENCES & ACKNOWLEDGEMENTS

Reference

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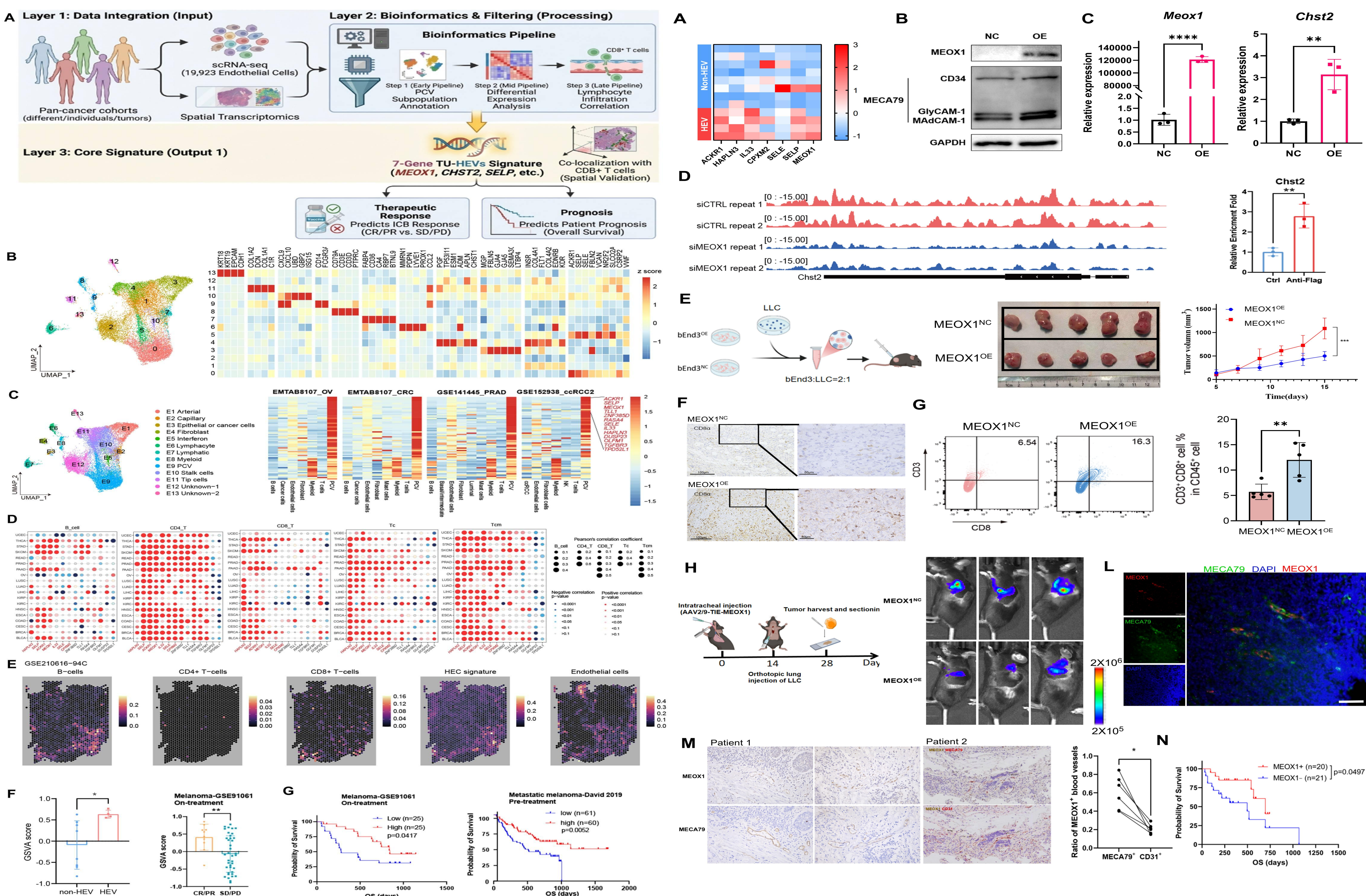
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RESULTS



TU-HEVs signature including MEOX1 was successfully established. In clinical cohorts, high signature scores significantly correlated with higher objective response rates (CR/PR) and prolonged overall survival (OS). Mechanistically, ChIP-seq and CUT&Tag confirmed MEOX1 directly binds the CHST2 promoter, activating its transcription and promoting peripheral node vascular addressin (PNAd) glycosylation essential for HEV maturation. In vivo, AAV-mediated endothelial-specific MEOX1 overexpression significantly increased MECA79⁺ TU-HEVs and CD8⁺ T cell infiltration, effectively suppressing tumor growth. Furthermore, clinical lung cancer samples exhibited prominent MEOX1 and MECA79 co-localization. Conclusions: The MEOX1-CHST2 transcriptional axis acts as a critical “molecular switch” driving the maturation of TU-HEVs. Upregulating MEOX1 expression via endothelial-targeted AAV can induce TU-HEVs maturation and promote lymphocyte infiltration, thereby effectively remodeling the immunosuppressive microenvironment. This approach offers a novel strategy for overcoming resistance to anti-angiogenic combined immunotherapy in solid tumors.