



P2.005: TGF- β -Driven Interplay Between THBS2⁺ CAFs and SPP1⁺ TAMs Promotes Immune Exclusion and Immunotherapy Resistance in Lung Adenocarcinoma

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INTRODUCTION

Cancer-associated fibroblasts (CAFs) are highly heterogeneous, comprising diverse subpopulations with distinct roles in cancer progression^[1,2]. Emerging evidence indicates that CAFs influence the tumor immune microenvironment (TIME), but the specific CAF subpopulation responsible for immune checkpoint inhibitor (ICI) resistance in lung adenocarcinoma (LUAD) remains undefined^[3,4].

METHODS

Design: We employed the Scissors algorithm to integrate bulk transcriptomic data with extensive phenotypic information and large-scale scRNA-seq (n=222) to identify CAF subclusters most associated with ICI response and post-treatment survival. Validated findings via spatial transcriptomics, immunofluorescence, and SPP1-cre murine models. Employed cytokine arrays, IP-MS, and functional assays to delineate THBS2-ITGB5-NF- κ B-IL6-SPP1 signaling axis and CD8⁺ T cell modulation mechanisms.

DISCUSSION AND CONCLUSION

This study provides an in-depth analysis of the dynamic interaction network between CAFs and immune cells, offering new insights into precise classification and personalized treatment of LUAD. We demonstrate that THBS2⁺ myCAFs and SPP1⁺ TAMs serve as synergistic drivers of immunosuppression. In clinical applications, combination strategies integrating ICI with targeted therapies, or interventions that reprogram immunosuppressive cellular components (e.g., TAMs and CAFs) prior to ICI administration, may represent promising therapeutic approaches for ICI-resistant patients.

REFERENCES & ACKNOWLEDGEMENTS

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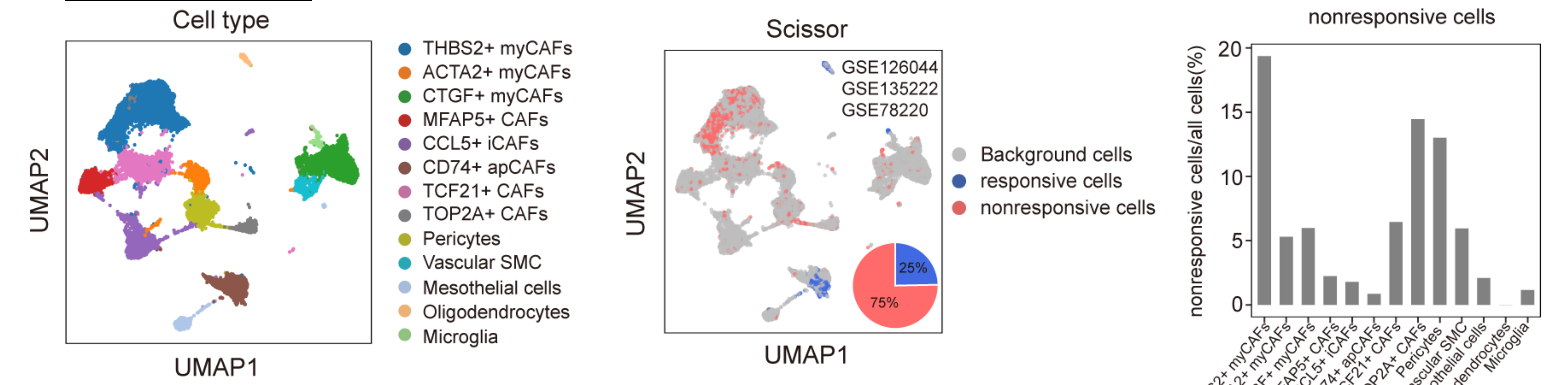
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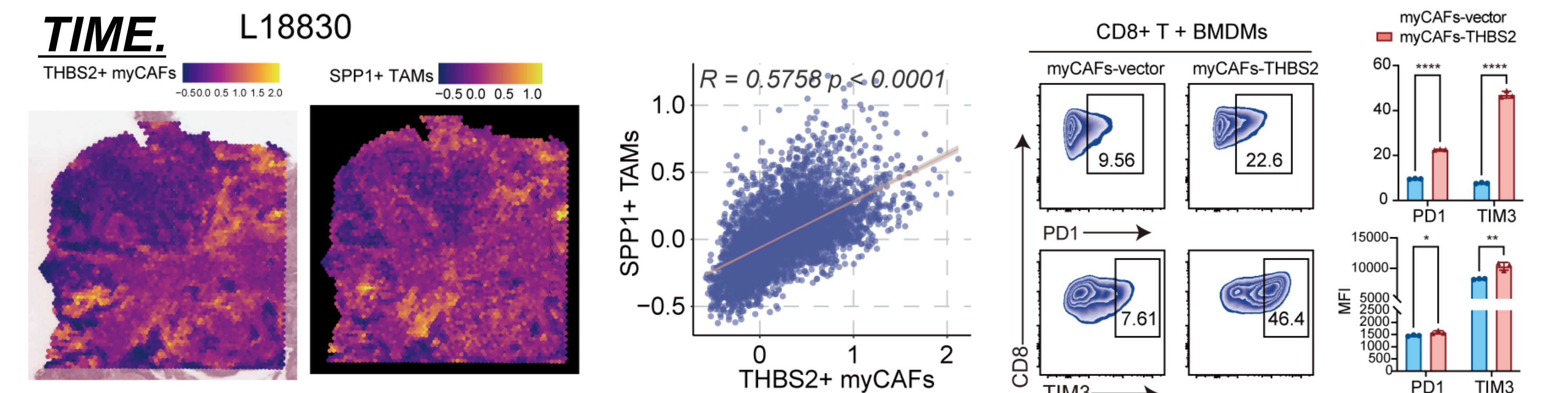
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RESULTS

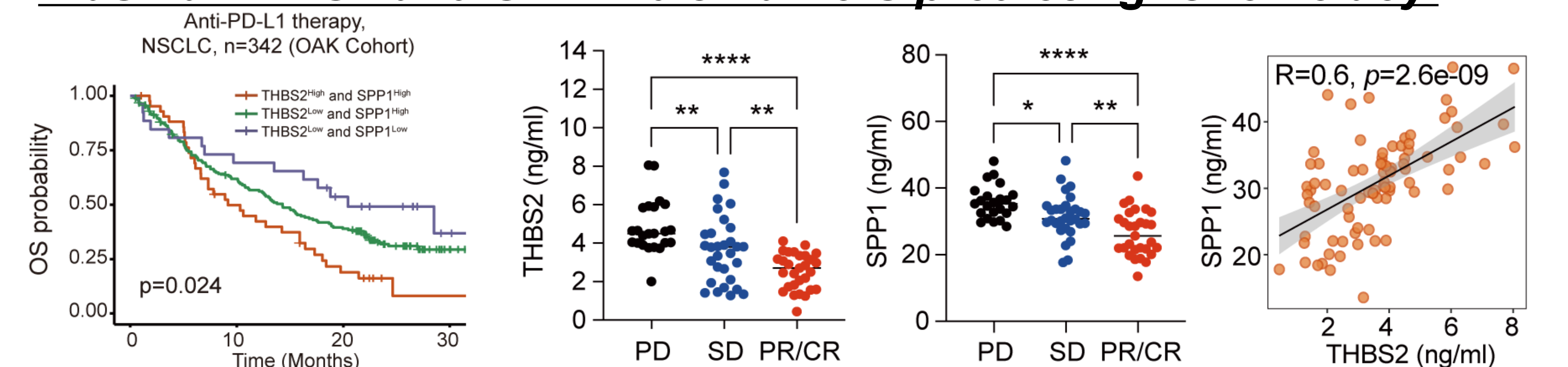
Multi-omics analysis reveals THBS2⁺ myCAFs associated with ICI resistance.



THBS2⁺ myCAFs interact with SPP1⁺ TAMs to create a suppressive TIME.



Plasma THBS2 and SPP1: biomarkers predicting ICI efficacy.



Combining AAV-shTHBS2 targeted therapy for fibroblasts with SPP1 neutralization can prolong survival and enhance LUAD sensitivity to immunotherapy.

