



PT1.02.05: CYR61 Secreted by NF2-Low Tumor Cells Suppresses AdiCAF Differentiation to Hinder Chemoimmunotherapy Efficacy in NSCLC

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INTRODUCTION

Neoadjuvant chemoimmunotherapy has redefined the management of resectable non-small cell lung cancer (NSCLC). However, at least half of the patients fail to achieve a major pathological response (MPR). How residual tumors restructure their local stroma to evade immune clearance remains unclear.

METHODS

We employed multi-omics approaches, including spatial transcriptomics and single-cell RNA sequencing (scRNA-seq), to comprehensively profile the tumor microenvironment of paired pre- and post-treatment NSCLC tissues. Tumor-stromal-immune crosstalk was investigated using in vitro co-culture models, and therapeutic interventions were evaluated in murine models.

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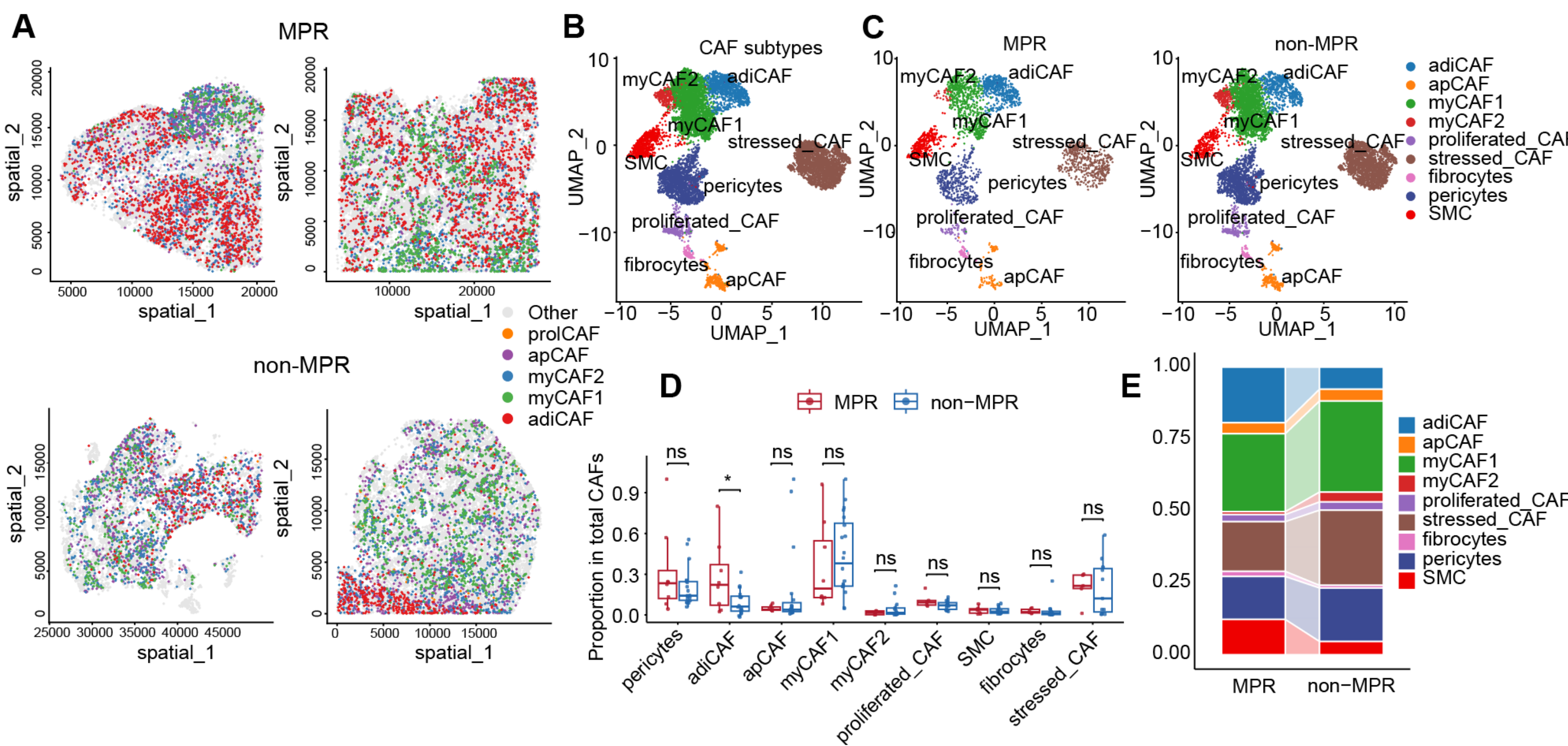
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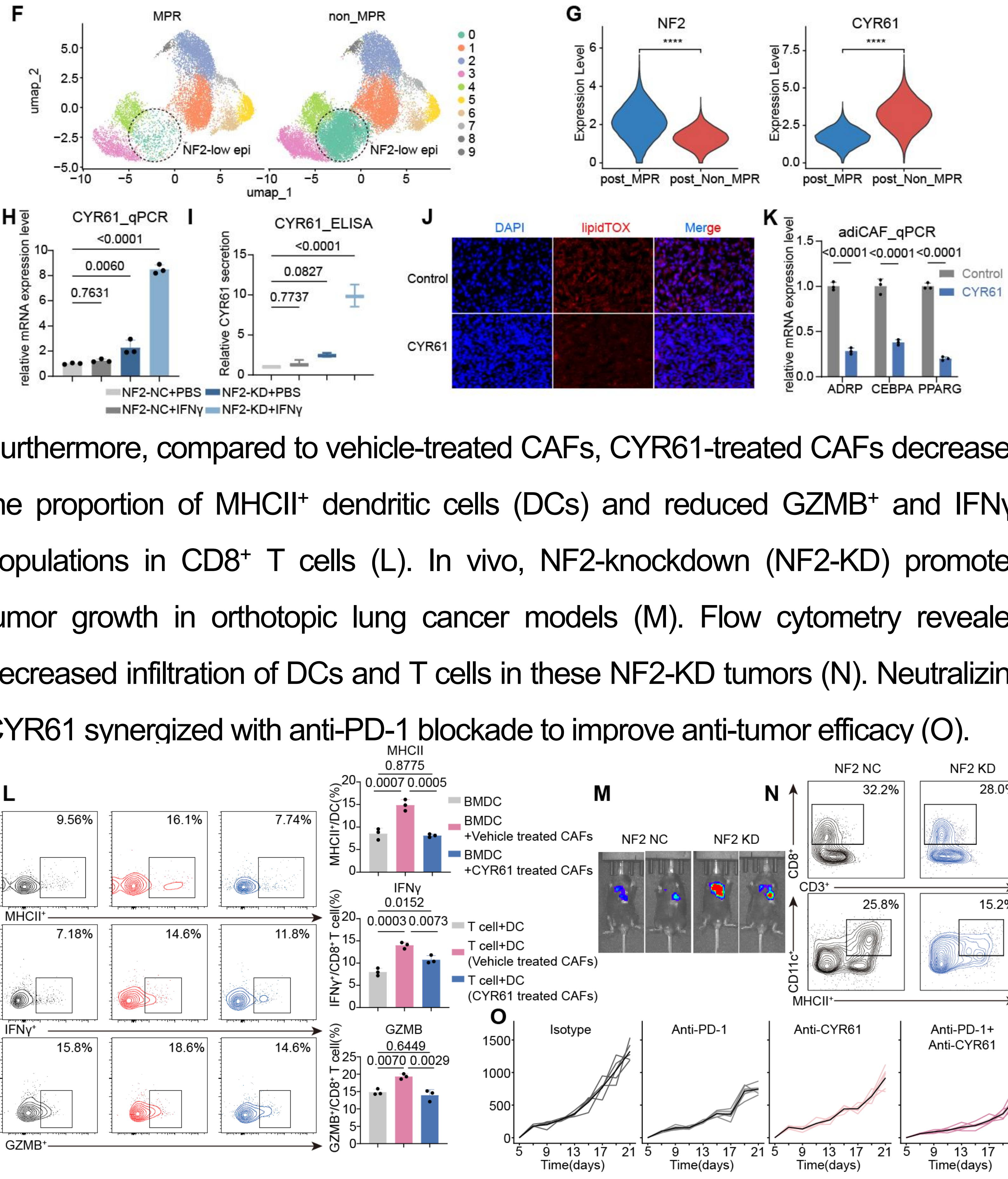
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No artificial intelligence (AI) tools were used in the development of this presentation.

RESULTS

Clinical multi-omics revealed spatial restructuring in non-MPR residual tumors, characterized by a significant reduction of the adipogenic cancer-associated fibroblast (adiCAF) subpopulation (A-E).



Concurrently, a residual tumor subpopulation emerged, defined by NF2-low expression and upregulation of CYR61 (F, G). Mechanistically, following PD-1 blockade, IFN γ released by activated T cells stimulated NF2-low tumor cells, leading to CYR61 transcription (H) and secretion (I). In vitro, CYR61 treatment suppressed adipogenic differentiation, evidenced by decreased LipidTOX fluorescence in cultured fibroblasts (J) and downregulation of the adiCAF-related signature (ADRP, CEBPA, PPARG) (K).



DISCUSSION AND CONCLUSION

In tumor samples from non-MPR patients, the significant reduction of the adiCAF subpopulation is driven by NF2-low tumor cells. Upon IFN γ stimulation, these tumor cells secrete CYR61 to block fibroblast adipogenic differentiation, ultimately mediating immune evasion and hindering therapeutic efficacy. Targeting the NF2-CYR61 axis to modulate this stromal remodeling offers a potential therapeutic strategy to enhance immunotherapy outcomes.