

P3.061-175 Targeting Pericyte MEF2D with a Novel Antisense Oligonucleotide Enhances the Efficacy of Lung Cancer Immunotherapy

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INTRODUCTION

- Tumor pericytes (TPCs) are key components of the tumor vasculature and potential regulators of antitumor immunity.
- However, how TPCs shape the tumor immune microenvironment and whether they represent actionable therapeutic targets remain poorly understood

DISCUSSION AND CONCLUSION

Actionable Take Away Message

- Pericyte-targeted MEF2D silencing enhances immunotherapy efficacy by promoting TLS maturation and remodeling the tumor immune microenvironment.

Future Direction for Research

- Establish biomarker-guided strategies to identify patients most likely to benefit from TPC-targeted MEF2D therapy.

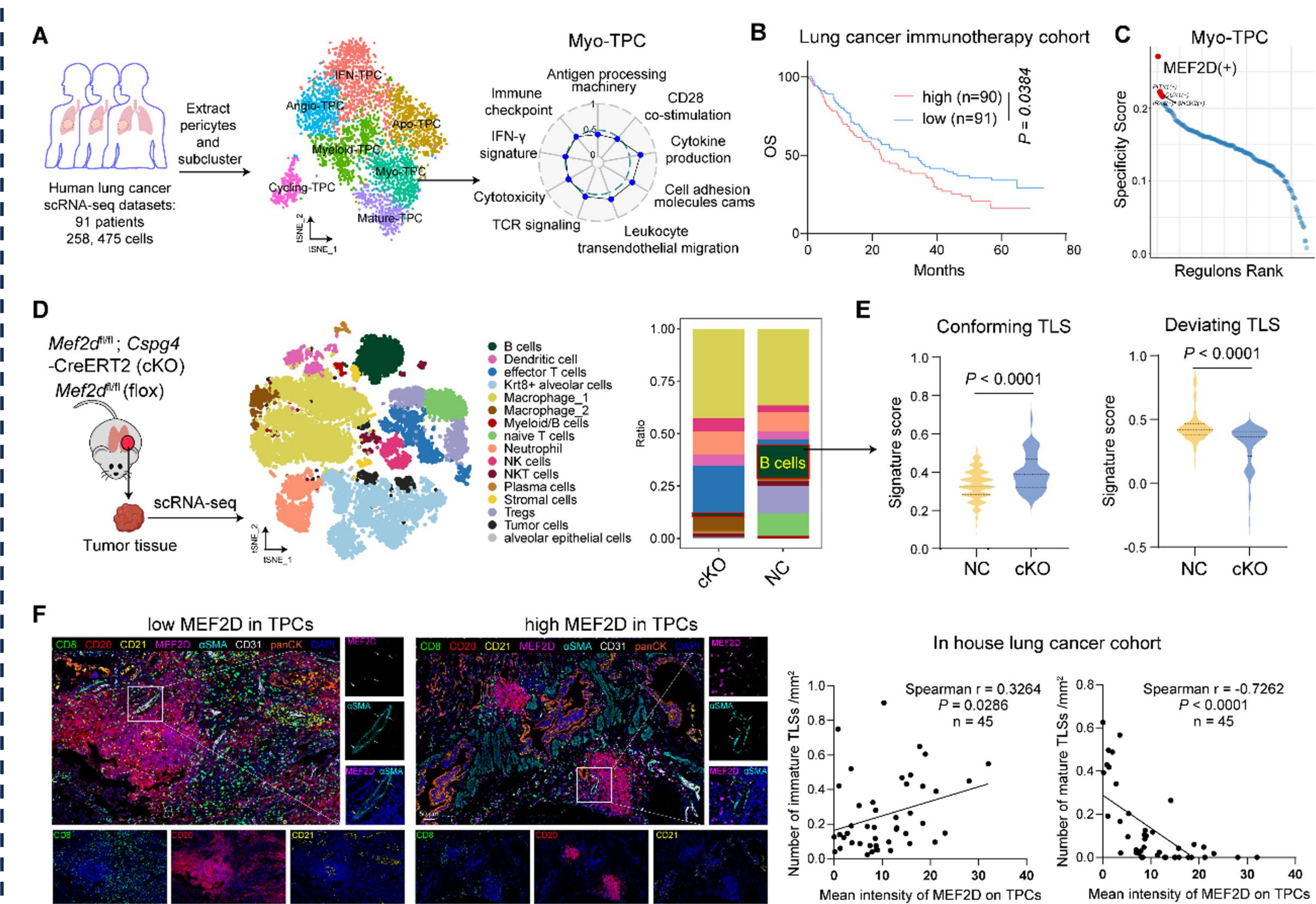
REFERENCES & ACKNOWLEDGEMENTS

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METHODS

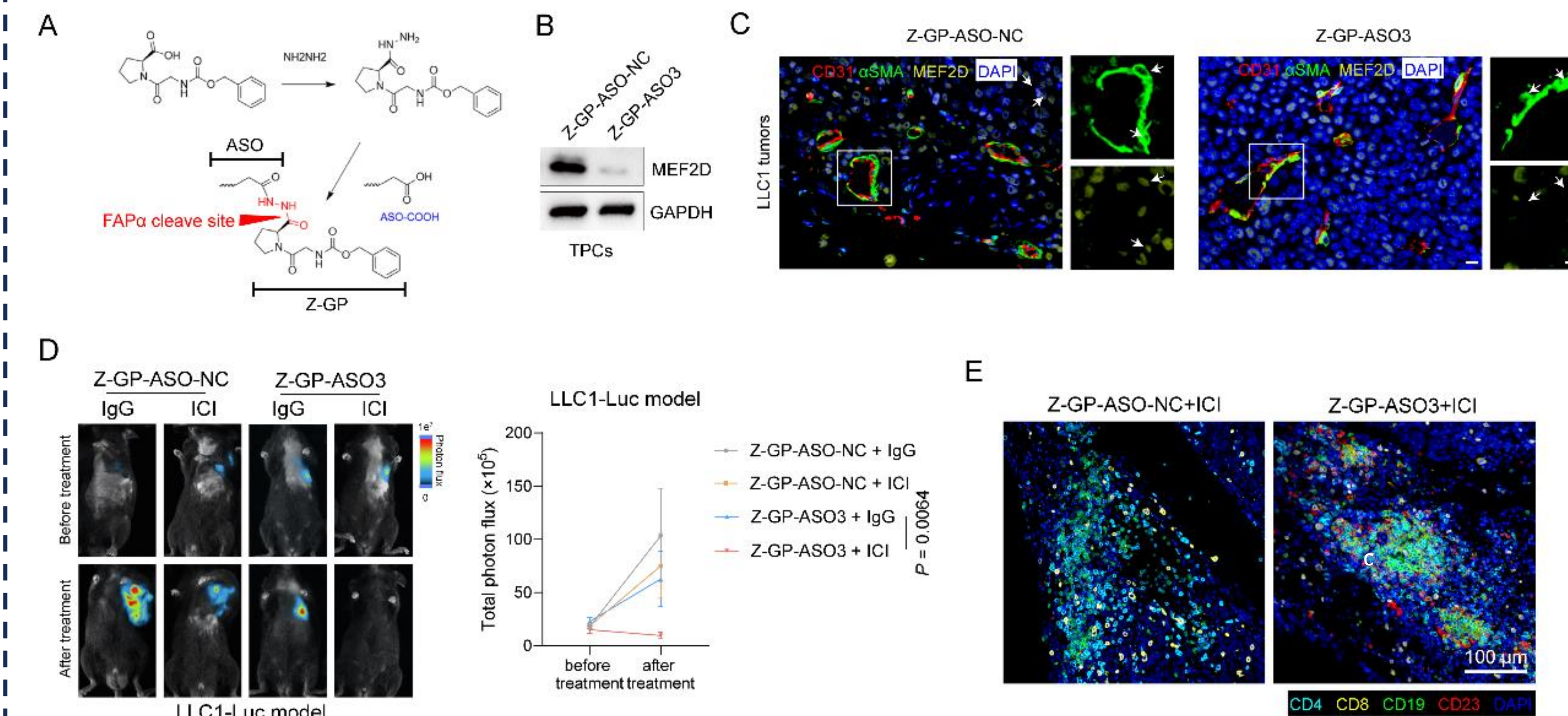
- scRNA-seq: Pericyte atlas construction and target validation.
- Targeted delivery: FAP α -responsive Z-GP-ASO prodrug development.
- Mass cytometry: TIME profiling.

RESULTS



Functional dissection of the pericyte landscape identified a myogenesis-associated subpopulation (myo-TPC) closely linked to an immunosuppressive TIME and inferior immunotherapy efficacy, with MEF2D acting as its pivotal regulator. Single-cell transcriptomic profiling revealed that pericyte-specific Mef2d depletion promoted a favorable TIME by realigning B-cell differentiation with the tertiary lymphoid structure (TLS) maturation trajectory. This was evidenced by a programmatic shift from a deviating-dominant phenotype

toward a high-conforming TLS signature. Consistently, high MEF2D expression in TPCs significantly correlated with a lower density of mature TLSs and an accumulation of immature structures in human lung cancer sections (Fig.1).



To address this, a pericyte-targeting prodrug (Z-GP-MEF2DASO) was developed, which effectively knocked down MEF2D in vitro and specifically reduced pericyte MEF2D levels in vivo. Z-GP-MEF2DASO significantly increased mature TLS density and enhanced the infiltration of cytotoxic CD8+T cells and NK cells, thereby activating the TIME. Consequently, Z-GP-MEF2DASO treatment effectively improved response to immunotherapy in vivo (Fig.2)