

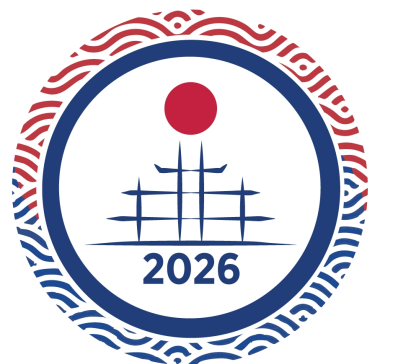


Endogenous CD155 Rewires Glycolysis via PI3K/AKT/HIF-1 to Drive Anti-PD-1 Resistance in NSCLC

Jin Bo Zhao¹, Wei Guang Du¹

Correspondence: zhaojinbo@aliyun.com

¹Department of thoracic surgery, Tangdu Hospital, Fourth Military Medical University, 569 Xinsi Road, Xi'an, 710038, Shaanxi, China



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INTRODUCTION

Lung cancer remains the leading cause of cancer-related mortality¹, with over half of patients exhibiting resistance to anti-PD-1 therapy². Compensatory interactions among immune checkpoints lead to the upregulation of inhibitory molecules such as TIM-3, TIGIT, CD155, and FGL-1, which attenuate the immune activation induced by anti-PD-1 therapy and promote malignant tumor progression, thereby driving resistance to PD-1 blockade³⁻⁵. This study investigates the role of CD155 in non-small cell lung cancer (NSCLC) and proposes a dual-targeting therapeutic strategy involving combined blockade of CD155 and PD-1.

METHODS

Molecular Expression Profiling

- Single-cell technologies were applied to investigate the interrelationships among immune checkpoints.
- Immunohistochemistry (IHC) and Western blotting were used to verify the expression levels of relevant molecules.

Cell Model Construction

- A CD155-knockout (KO) NSCLC cell line was generated using the CRISPR-Cas9 system.

Multi-omics Systematic Analysis

- Integrative multi-omics profiling, including single-cell RNA-seq, bulk RNA-seq, proteomics, and metabolomics, was performed on KO cells to elucidate the functional roles of CD155 in NSCLC.

Key Molecular Validation

- Critical molecular events were further validated via IHC, Western blotting, and chromatin immunoprecipitation (ChIP).

Functional and Therapeutic Efficacy Assessment

- In vitro*: Cell proliferation, migration, and glucose metabolic phenotypes were examined.
- In vivo*: The AAV9_shCD155 vector was administered in animal models, alone or in combination with 2-DG or pembrolizumab, to evaluate antitumor efficacy and immune infiltration.

DISCUSSION AND CONCLUSION

This study demonstrates that CD155 overexpression in NSCLC activates the PI3K/AKT/HIF-1 α pathway to upregulate glycolytic enzymes (GLUT1, GLUT3, LDHB), driving proliferation, migration, and metabolic reprogramming, while concurrently promoting an immunosuppressive microenvironment that mediates resistance to anti-PD-1 therapy. Multi-omics identified ETS1 as an upstream regulator and revealed CD155 directly binds ALDOA, suggesting precise glycolytic control. *In vivo*, combination of AAV9_shCD155 and pembrolizumab overcame resistance, suppressed tumor growth, and enhanced immune infiltration. Although further investigation of CD155 - PD-L1 crosstalk and cell-specific functions is required, this study is the first to establish CD155 as a dual metabolic-immune hub central to NSCLC resistance. Collectively, our findings provide a robust preclinical rationale for dual targeting of CD155 and PD-1.

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RESULTS

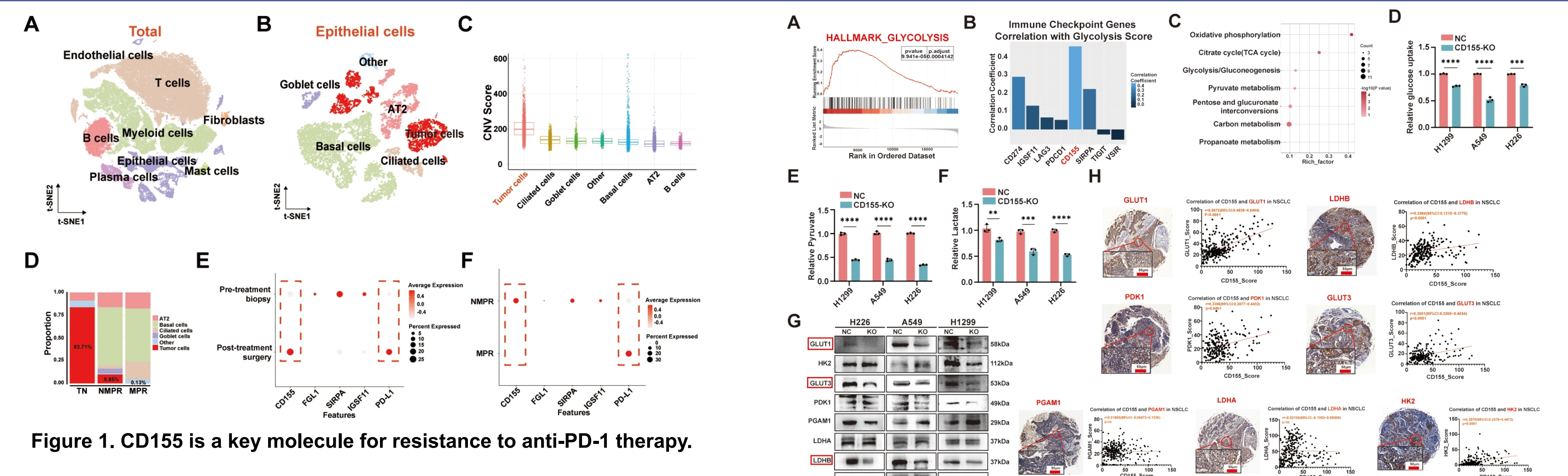


Figure 1. CD155 is a key molecule for resistance to anti-PD-1 therapy.

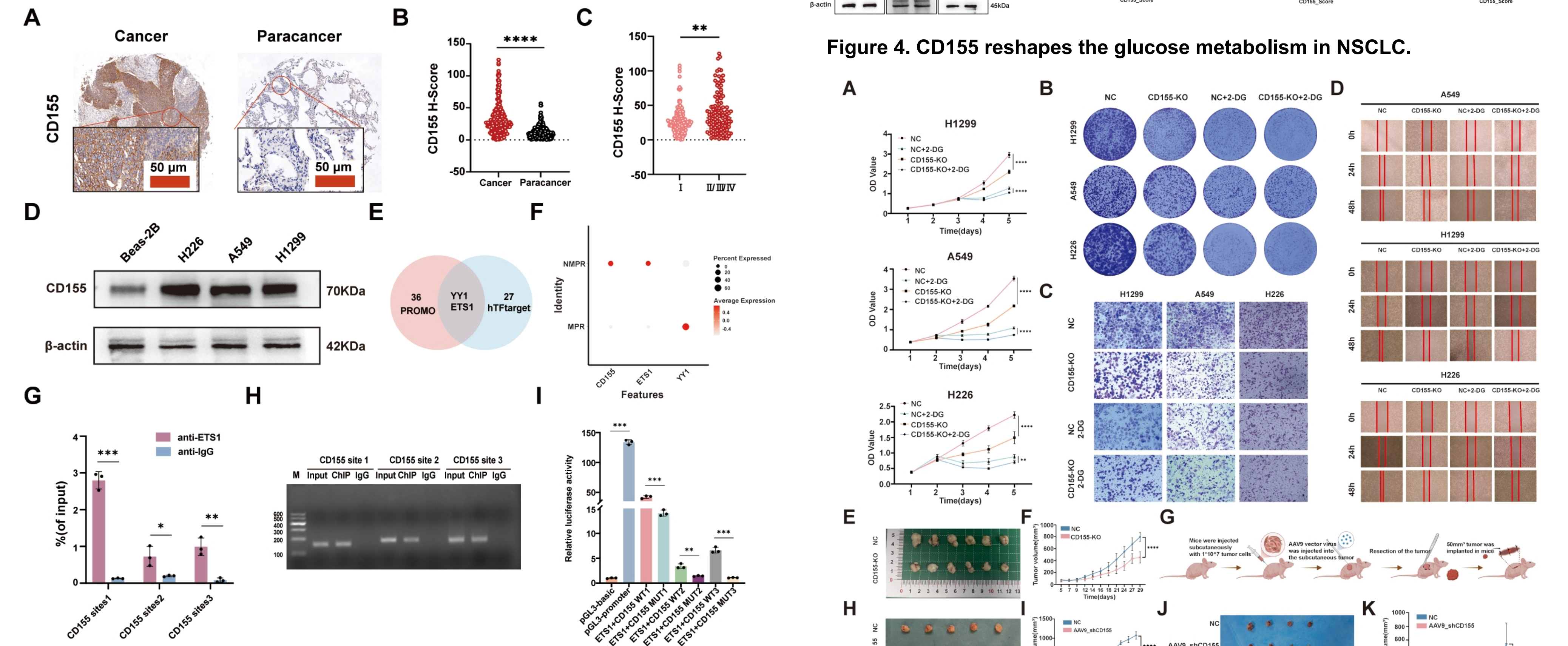


Figure 2. CD155 is transcriptionally regulated by ETS1 and associated with adverse patient outcomes.

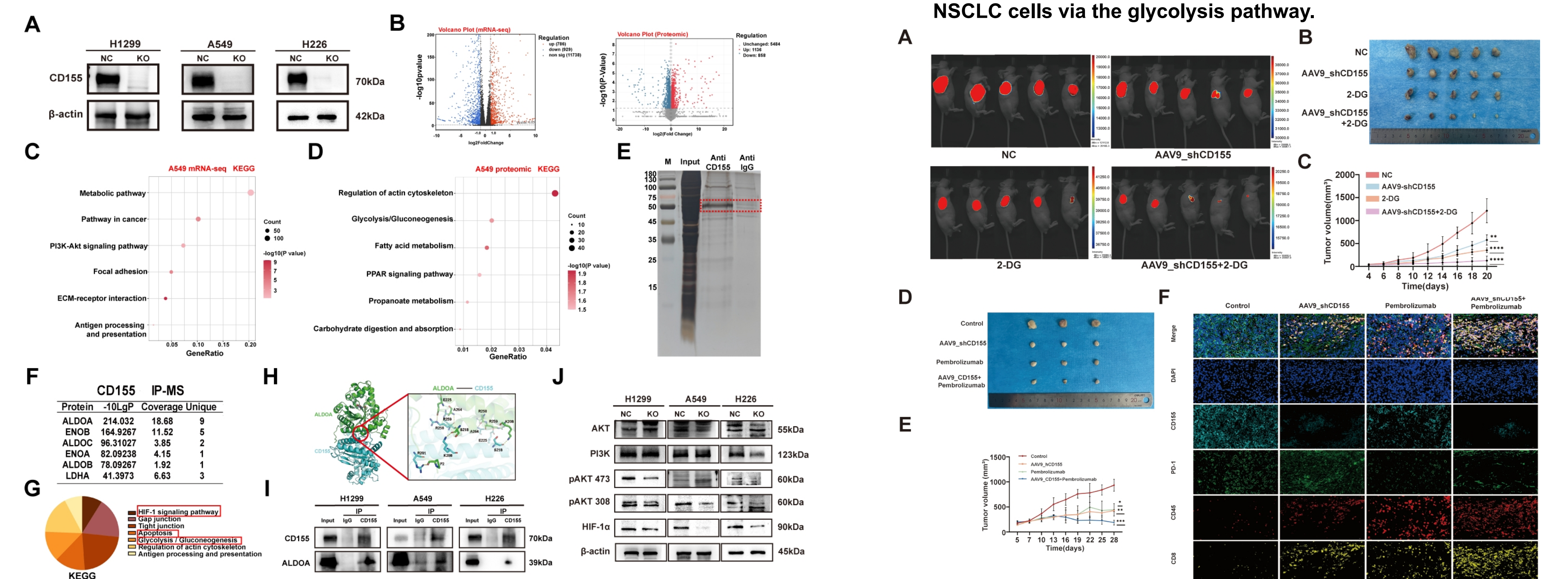


Figure 3. CD155 regulates gene expression, interacts with ALDOA, and activates the PI3K/AKT/HIF-1 α axis in NSCLC.

Figure 4. CD155 reshapes the glucose metabolism in NSCLC.

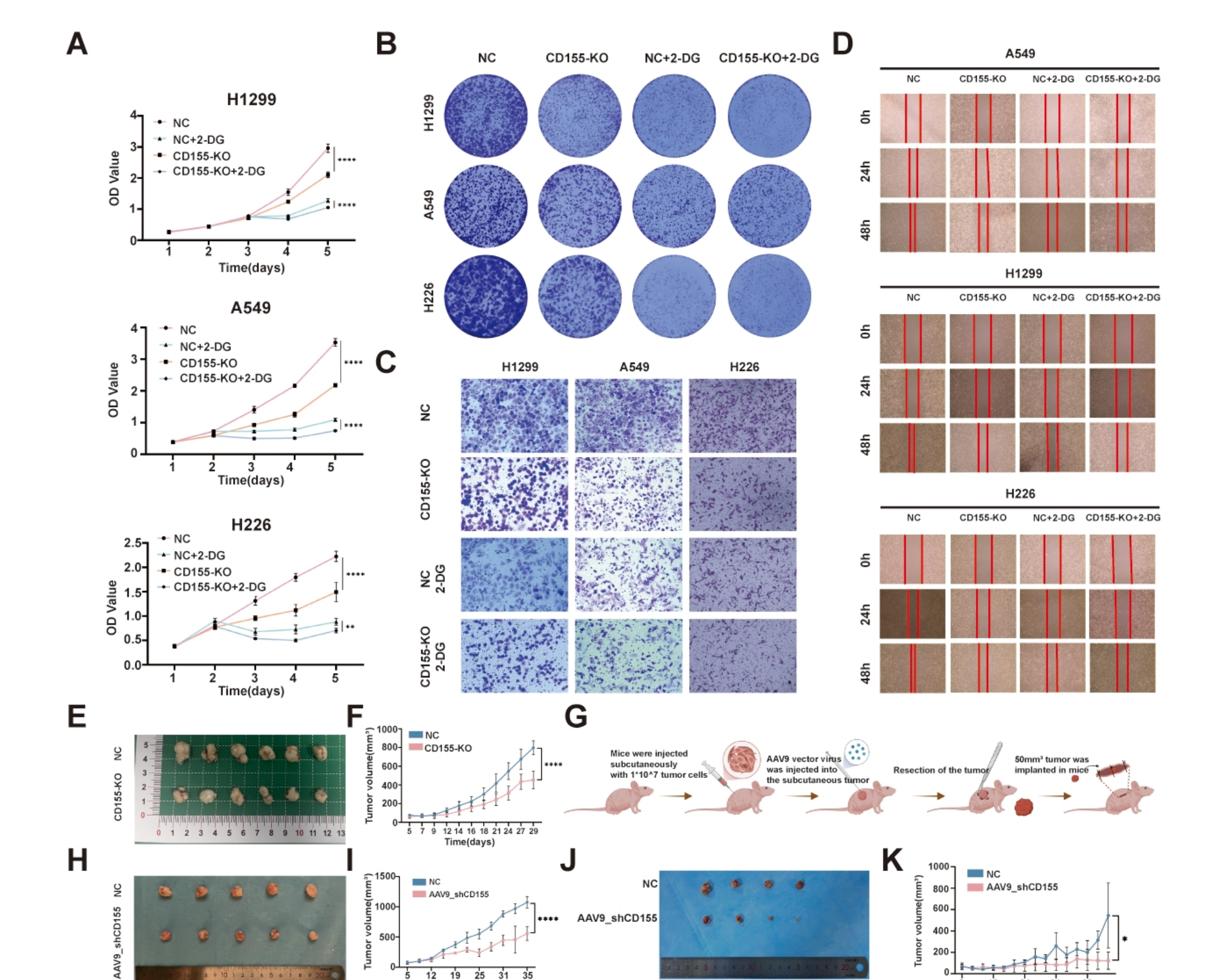


Figure 5. CD155 promotes the proliferation and metastatic phenotype of NSCLC cells via the glycolysis pathway.

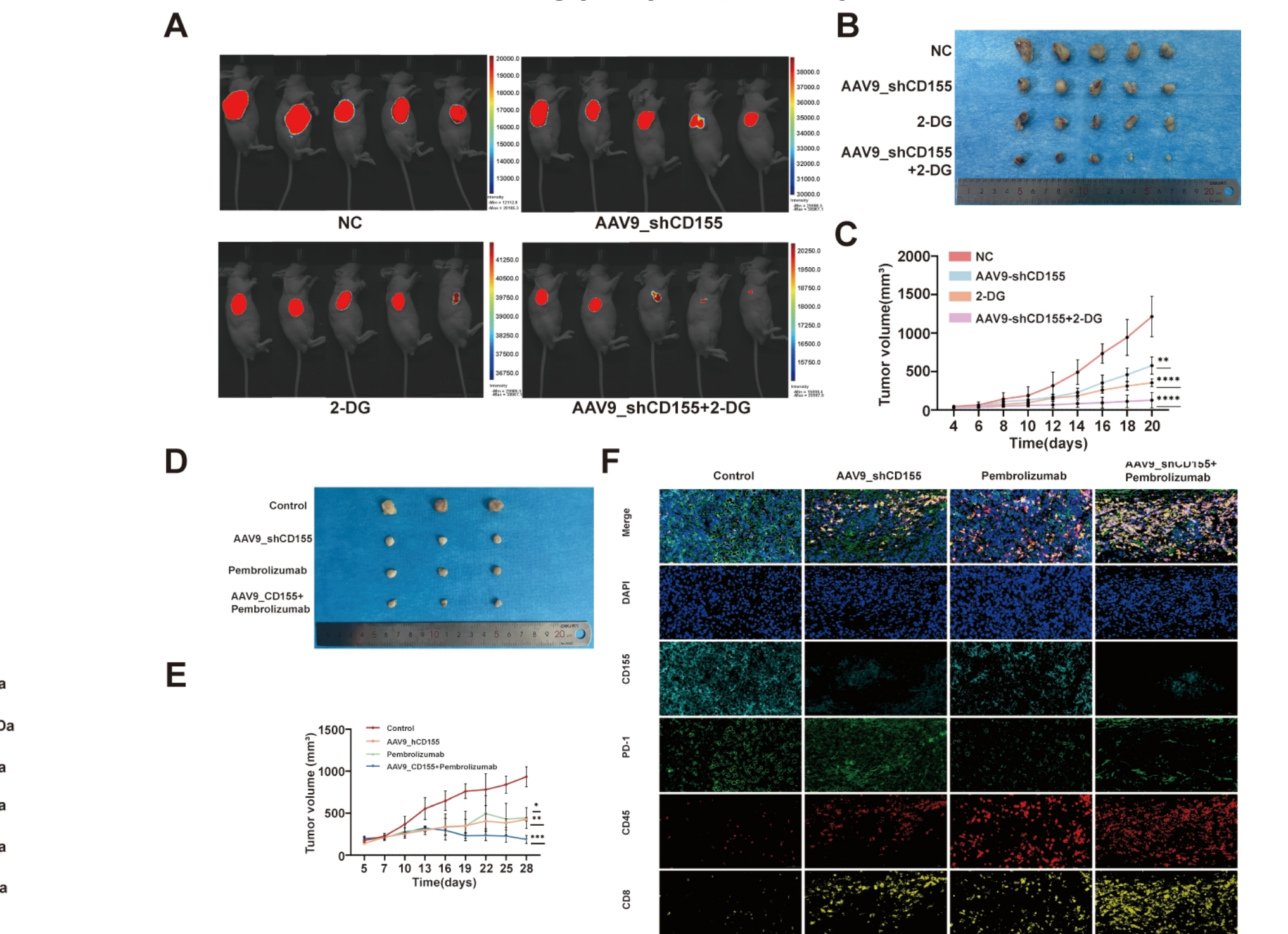


Figure 6. Targeting CD155 synergises with anti-PD-1 to inhibit tumour growth and promote immune infiltration.