



P2.028: TMT1A inhibits lung adenocarcinoma progression by suppressing M2 macrophage polarization

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INTRODUCTION

The involvement of human Thiol Methyltransferase 1A (TMT1A) protein has been reported in the development of several tumours. However, its role in tumour progression and immune microenvironment of lung adenocarcinoma (LUAD) have not been fully elucidated.

METHODS

Gene expression analysis and survival prognosis of TMT1A were used. Cell culturing, human tissue microarray, co-expression network and gene enrichment analysis were also carried out to focus on TMT1A expression. The Tumour Immune Single-Cell Hub was employed to categorize malignant, immune, stromal, and various other cell types within the tumour microenvironment. T Cell Proliferation and Activation Assay, qRT-PCR and siRNA were used to testified the interaction of TMT1A and immune cells. Finally, mouse xenograft was used to demonstrated the tumor depression function of TMT1A.

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DISCUSSION AND CONCLUSION

Actionable Take Away Message

Our findings revealed that TMT1A exhibits significantly downregulated expression in LUAD and functionally suppresses malignant phenotypes through the regulation of the P53 pathway. Moreover, TMT1A expression attenuated M2 polarization of TAMs and simultaneously enhancing T-cell activation. These findings position TMT1A as a promising therapeutic target for LUAD treatment.

Future Direction for Research

High TMT1A expression was found to inhibit M2 macrophage polarization and downregulate PD-L1 expression in LUAD cells. TMT1A expression has the potential ability to enhance immune responses and inhibit oncogenic processes, ultimately contributing to improved patient outcomes. Future orientation should be focused on the manipulation of TMT1A gene and protein expression and thereafter altering the therapeutic effect that immunotherapy may have on LUAD patients.

RESULTS

- Analysis of clinical samples and public databases revealed significantly lower TMT1A expression in tumorous LUAD samples as opposed to their non-neoplastic counterparts(**Fig. 1**).
- Cox regression analysis confirmed TMT1A as an independent prognostic factor for LUAD. Phenotypically, functional assays demonstrated that TMT1A expression inhibited LUAD cell proliferation, cell cycle, invasion and migration (**Fig. 2**).
- Furthermore, single cell transcriptome sequencing analysis showed that TMT1A expression was positively correlated with the immune cells, especially for macrophages(**Fig. 3**).
- Mechanistically, high TMT1A expression was found to inhibit M2 macrophage polarization and downregulate PD-L1 expression in LUAD cells(**Fig. 4**).
- In co-culture experiments involving LUAD cells and T cells, TMT1A knockdown suppressed T cell activation and reduced IFN- γ secretion. These findings were further validated by *in vivo* experiments, where TMT1A expression was found to promote CD8+ T cell infiltration in LUAD(**Fig. 5-6**).

Fig. 1

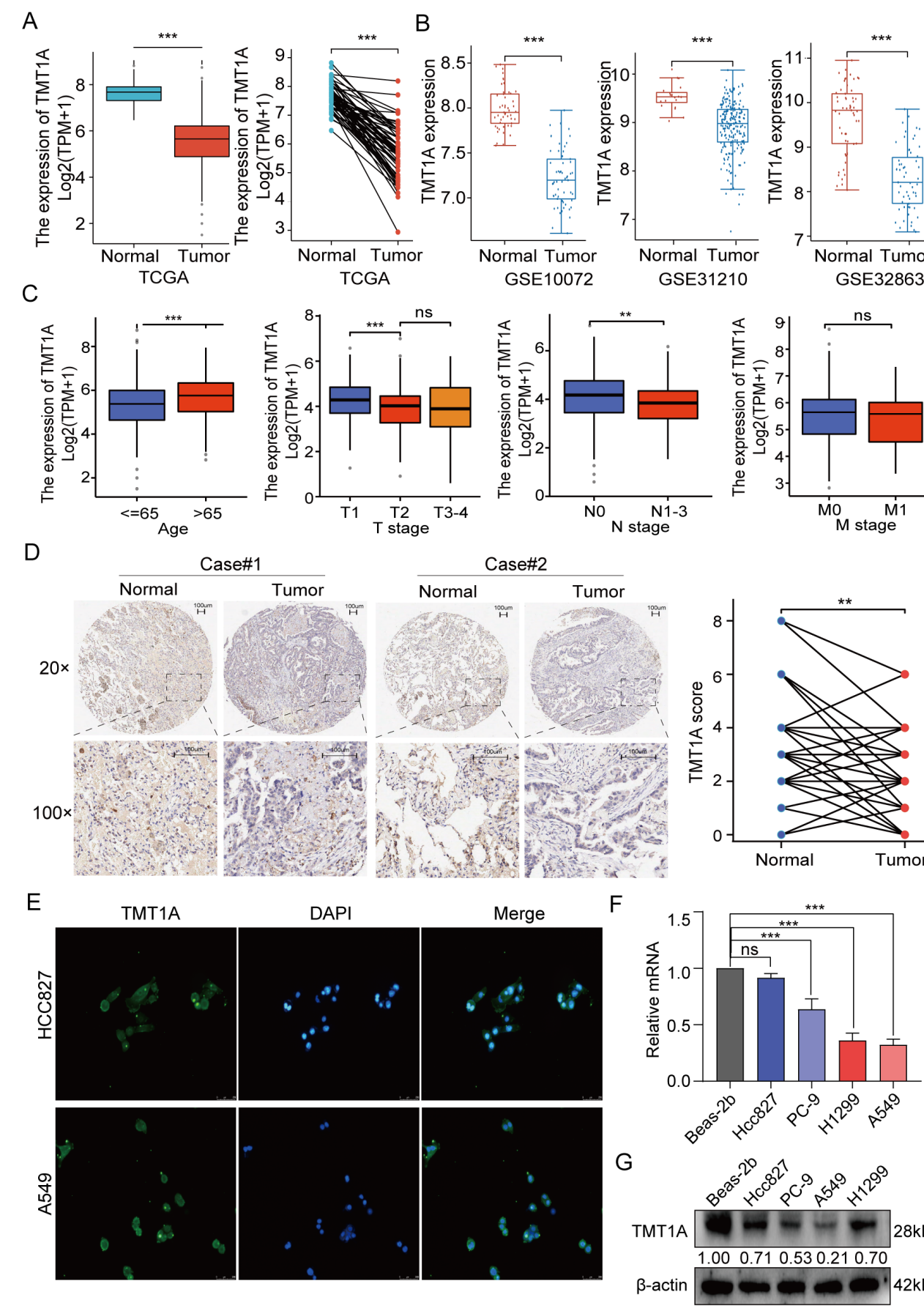


Fig. 2

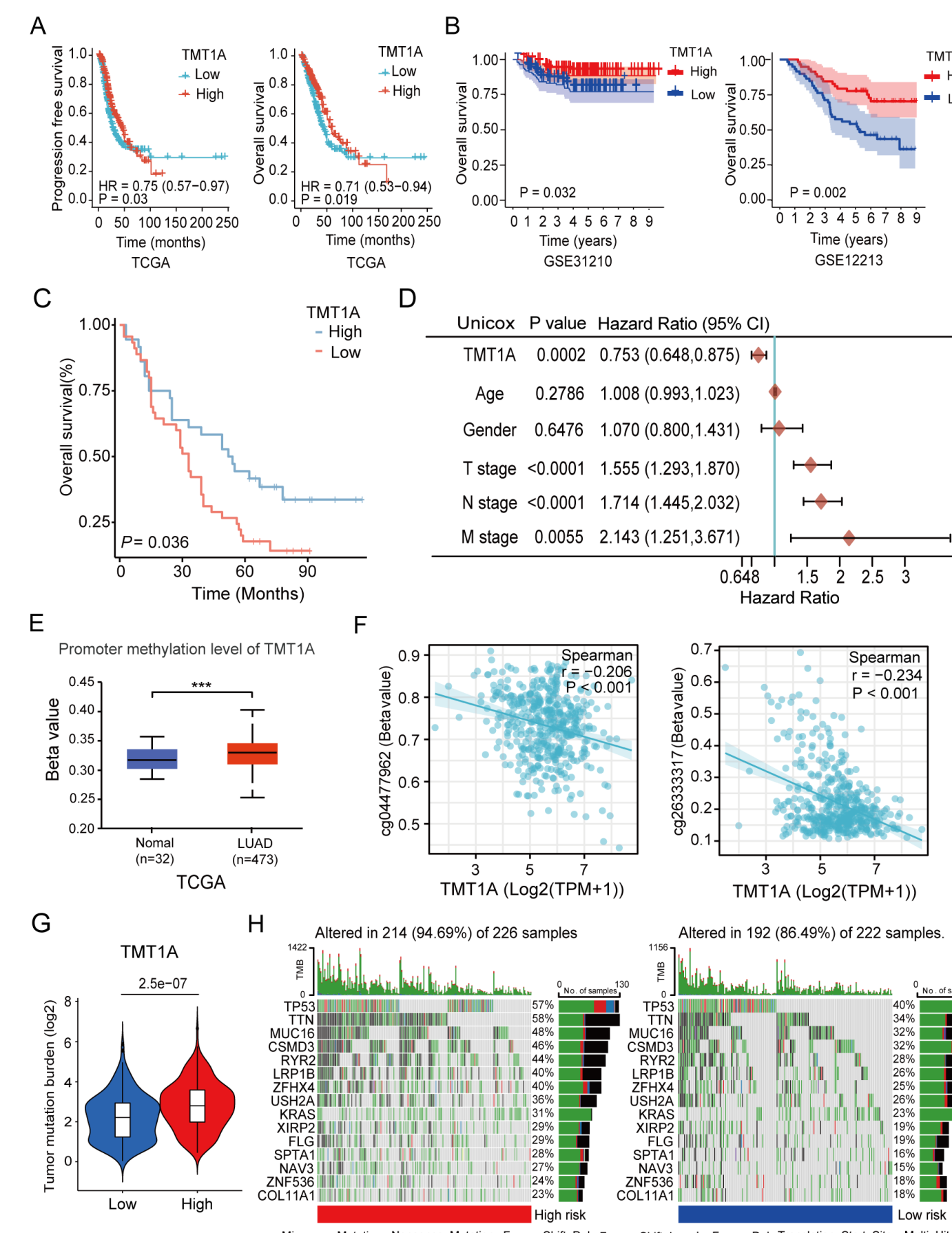


Fig. 3

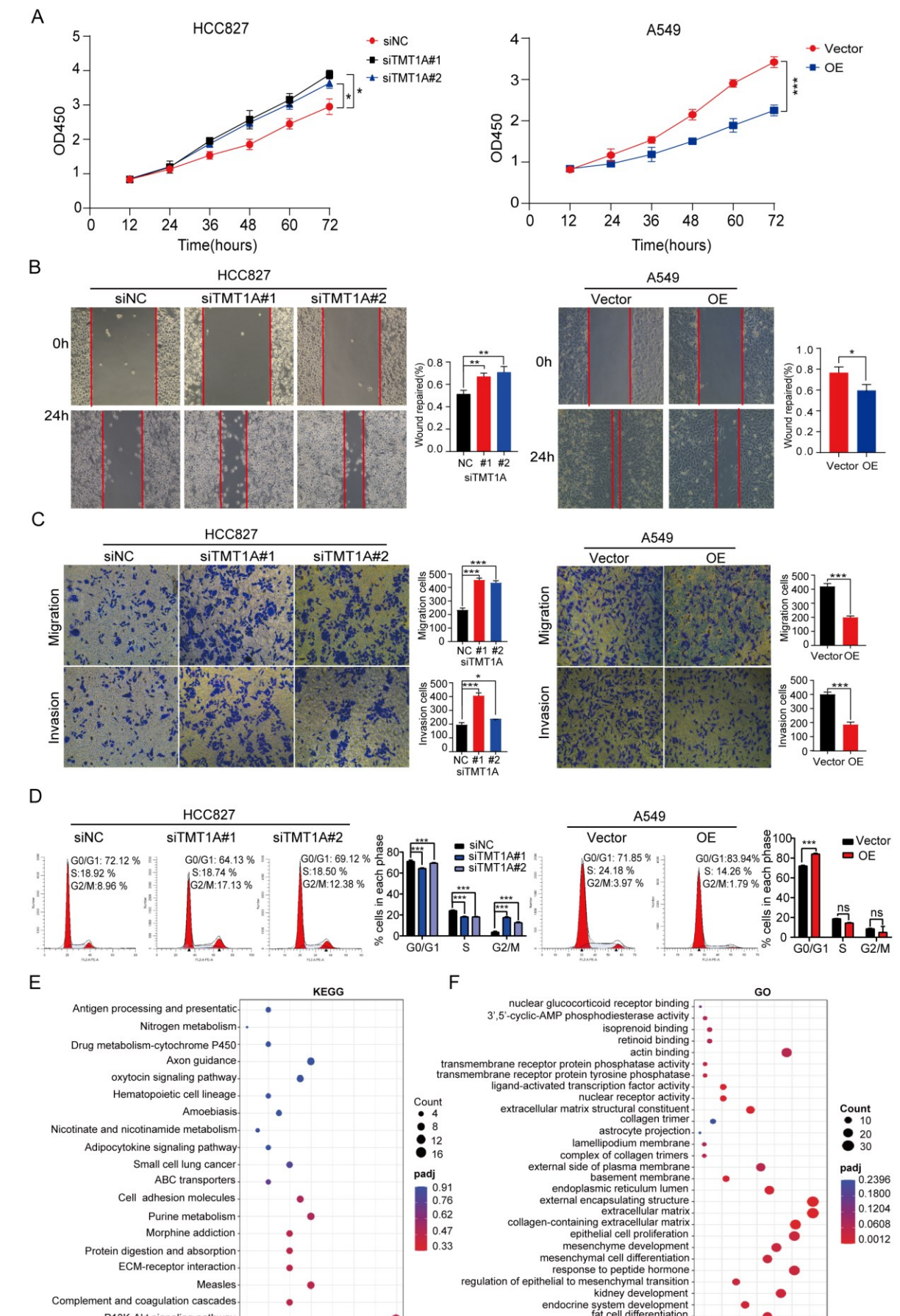


Fig. 4

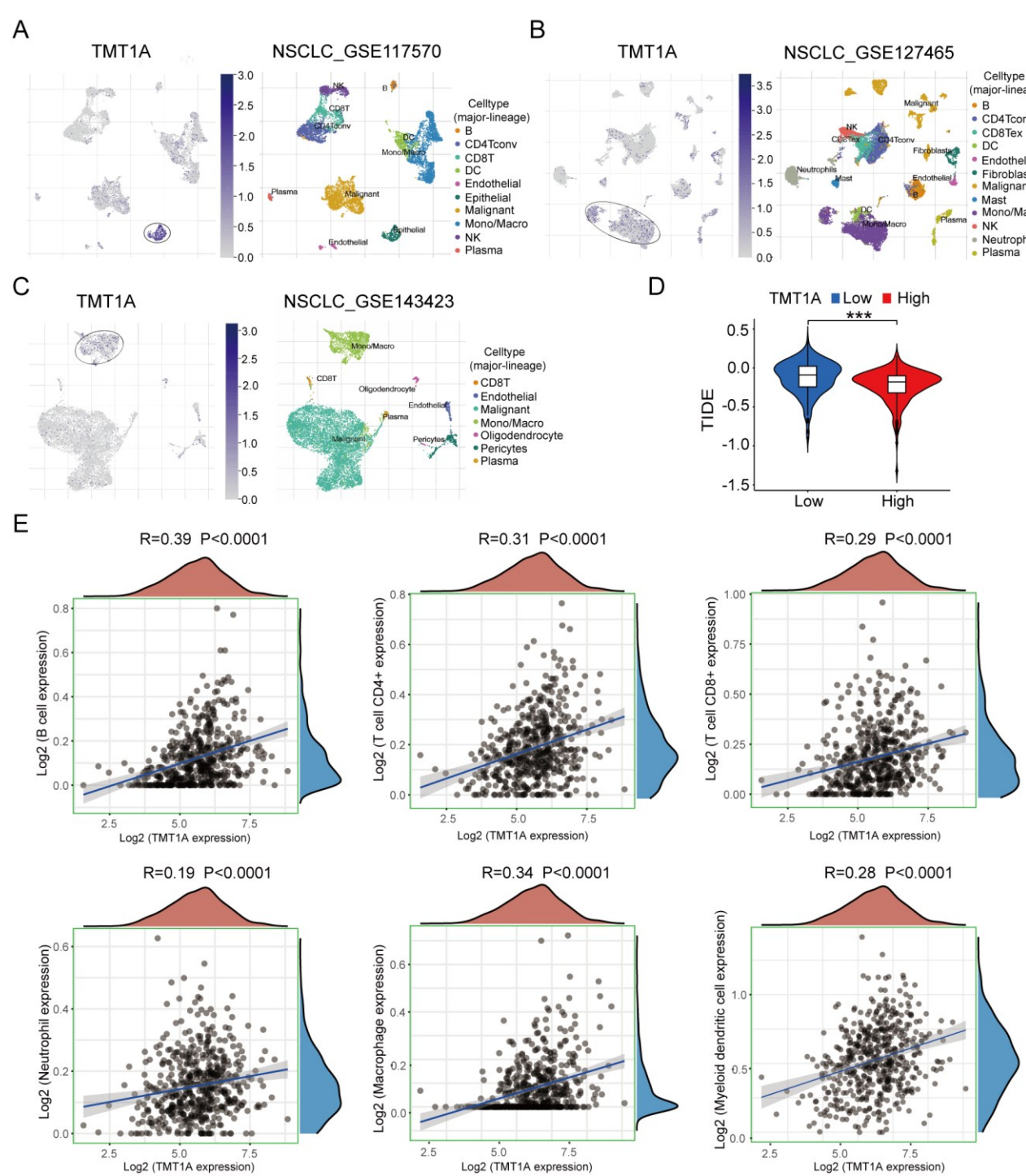


Fig. 5

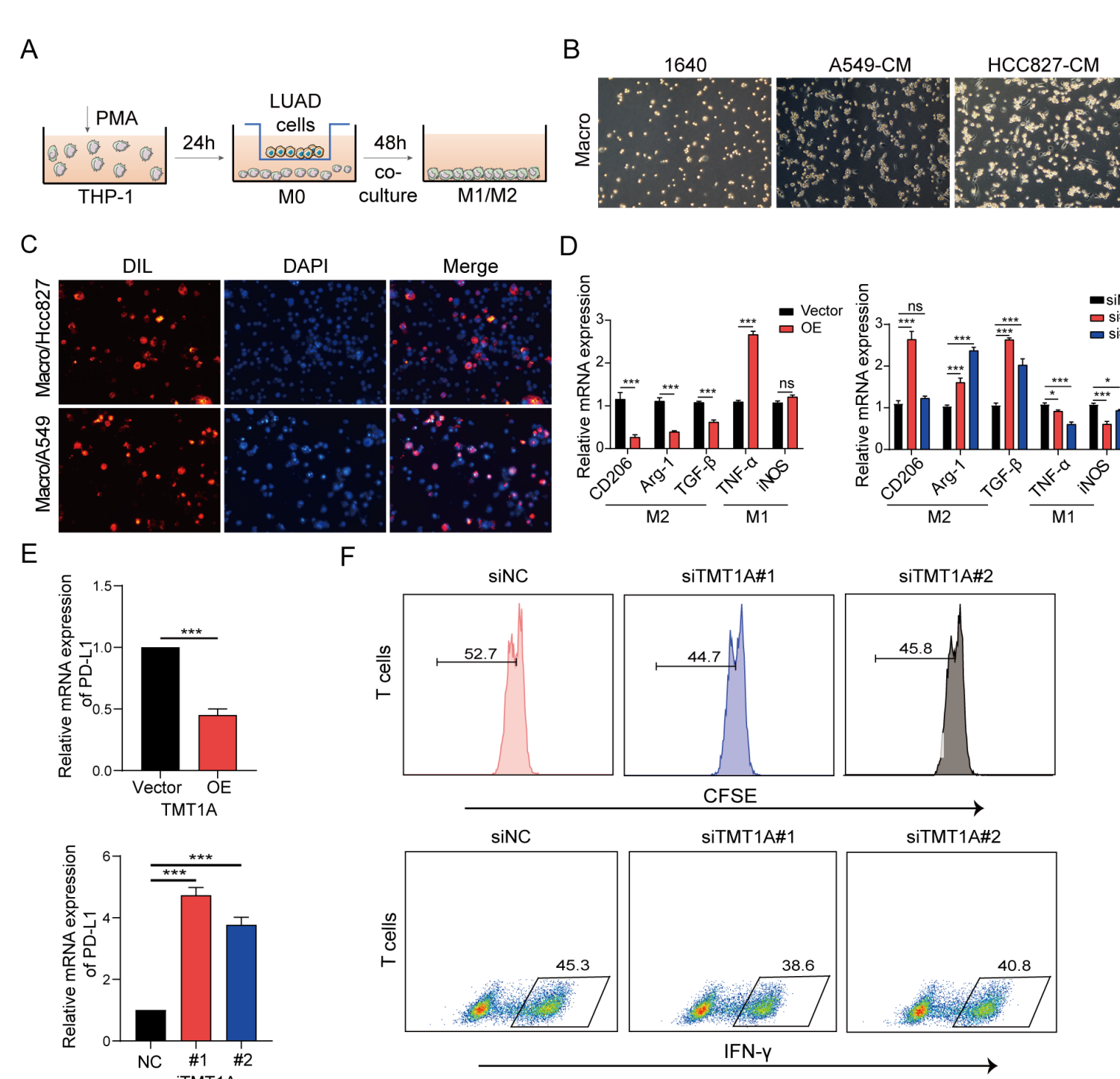


Fig. 6

