

INTRODUCTION

- Brain metastasis (BM) from EGFR wild-type lung adenocarcinoma (LUAD) is associated with **poor prognosis, limited targeted options, and a highly restrictive tumor immune microenvironment (TIME).**
- Glycosylated RNA (glycoRNA)** has emerged as an immune-regulatory molecule, but its role in **BM progression** remains unclear.
- We investigated how **metabolic reprogramming drives glycoRNA-mediated immune evasion** and whether this pathway can be therapeutically targeted.

METHODS

- Integrated analyses**
- scRNA-seq from 12 primary tumors and clinical ¹⁸F-FDG PET/CT from 176 patients.

- Molecular validation**
- glycoRNA-seq and ARPLA in 292 and 292Brm3 cell lines.

- Functional models**
- Reconstituted BBB model, syngeneic/xenograft brain metastasis mouse models, and PDOs.

- Endpoints**
- BM progression, angiogenesis, macrophage polarization, Siglec-15 binding, and response to Tislelizumab ± Tunicamycin (TM).

DISCUSSION AND CONCLUSION

Actionable Take Away Message

- Metabolic rewiring in BM fuels tRNA-Gly-CCC N-glycosylation and promotes an immunosuppressive niche through Siglec-15⁺ TAMs.
- Cell-surface glycosylated tRNA-Gly-CCC is a potential biomarker of poor outcome and immunotherapy resistance.
- Targeting N-glycosylation or combining it with Siglec-15 blockade may improve treatment efficacy in EGFR WT LUAD brain metastasis.

Future Direction for Research

- Validate these findings in larger, independent patient cohorts and paired primary/BM specimens.
- Define the downstream glycoRNA–Siglec-15 signaling mechanism in macrophages.
- Develop rational combination strategies integrating glycosylation inhibition with immune checkpoint blockade.

REFERENCES & ACKNOWLEDGEMENTS

- Xu M, Yu Y. WCLC 2026 abstract.
- Additional references available upon request.

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RESULTS

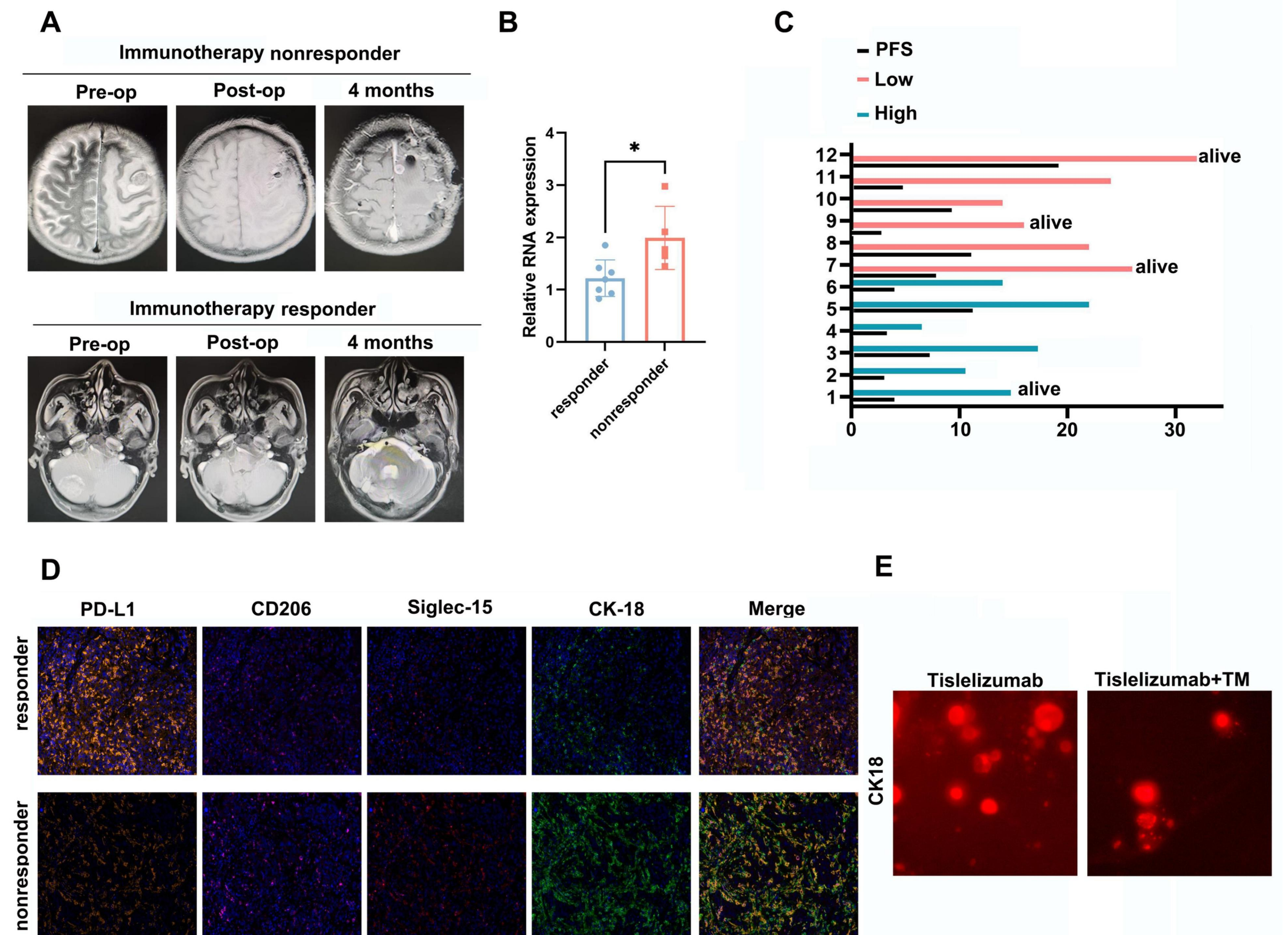


Figure 1. Therapeutic potential of targeting tRNA-Gly-CCC N-glycosylation in BM.

(A) MRI of immunotherapy responders vs. non-responders. (B) RT-qPCR of cell-surface glycosylated tRNA-Gly-CCC. (C) Survival analysis stratified by tRNA glycosylation. (D) mIF staining of immune markers. (E) Organoid response to Tislelizumab ± Tunicamycin (TM).

Key Findings

- BM hyperglycolysis:** ↑GLUT1 and ↑SUVmax, with poorer survival.
- GlycoRNA remodeling:** ↑UDP-GlcNAc and surface **N-glycosylated tRNA-Gly-CCC**.
- Metastatic function:** tRNA-Gly-CCC silencing ↓BBB extravasation, angiogenesis, and M2 recruitment.
- Immune mechanism:** **Siglec-15⁺ TAMs** were the major glycoRNA-interacting myeloid cells; tRNA depletion ↓Siglec-15 binding.
- Mitochondrial injury:** GlycoRNA depletion induced cristae loss and matrix swelling in macrophages.
- Therapeutic relevance:** High glycosylated tRNA predicted ICI resistance; **Tunicamycin restored Tislelizumab sensitivity.**