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Epithelial–mesenchymal transition (EMT) Signature Score of a Bulk Tumor May Not Reflect the EMT of Malignant Epithelial Cells

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Background

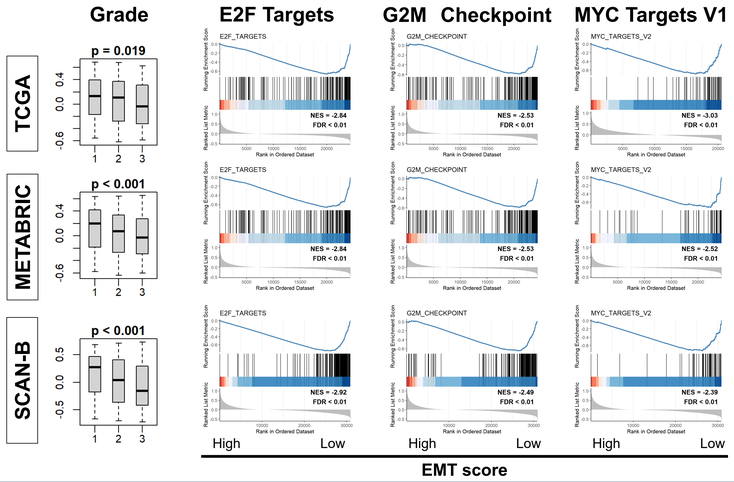
Epithelial–mesenchymal transition (EMT) is a process in which polarized epithelial cells acquire mesenchymal features, contributing to tumor progression, metastasis, and treatment resistance (1). Our group has shown the clinical relevance of pathway activity scores generated by GSVA of Hallmark gene sets in breast cancer (2,3). Based on this, we hypothesized that breast tumors with high EMT scores would display more aggressive biological features and poorer outcomes than EMT-low tumors.

Material & Methods

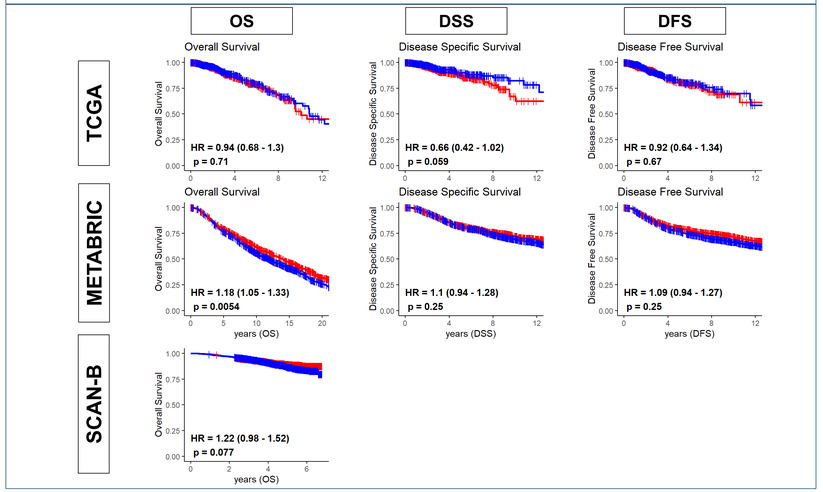
We analyzed three large breast cancer cohorts: TCGA (n=1,077), METABRIC (n=1,904), and SCAN-B (n=3,069). Survival outcomes (OS, DSS, DFS) were assessed. The tumor immune microenvironment was analyzed using xCell and Thorsson et al.'s immune metrics (4). Chemosensitivity was evaluated across four neoadjuvant datasets (GSE21094, GSE22358, GSE25066, GSE32646). Mutation burden and neoantigen load were also examined. To evaluate EMT signatures across cell types, single-sample GSEA was applied to single-cell RNA-seq data. EMT scores were generated by GSVA of the Hallmark EMT gene set (5), and each cohort was divided into EMT-high and EMT-low groups using the median as the cutoff.

Results

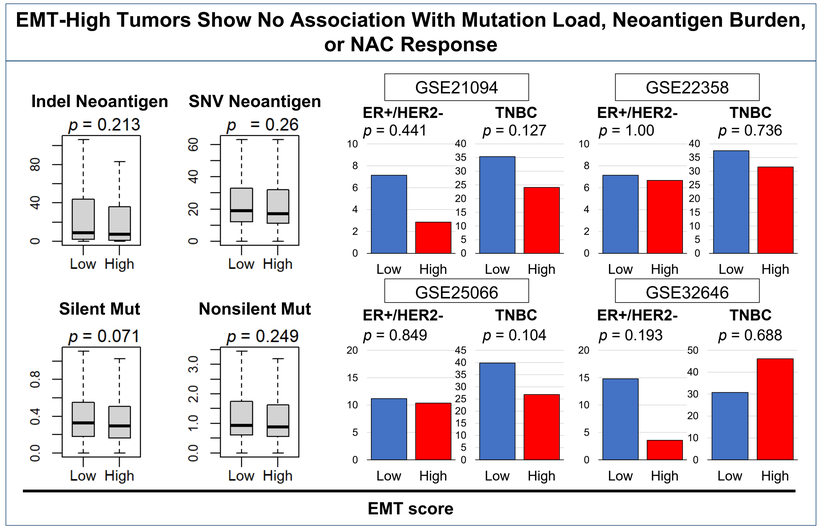
EMT-High Tumors Exhibit Lower Histological Grade and Suppressed Proliferation Pathway Activity



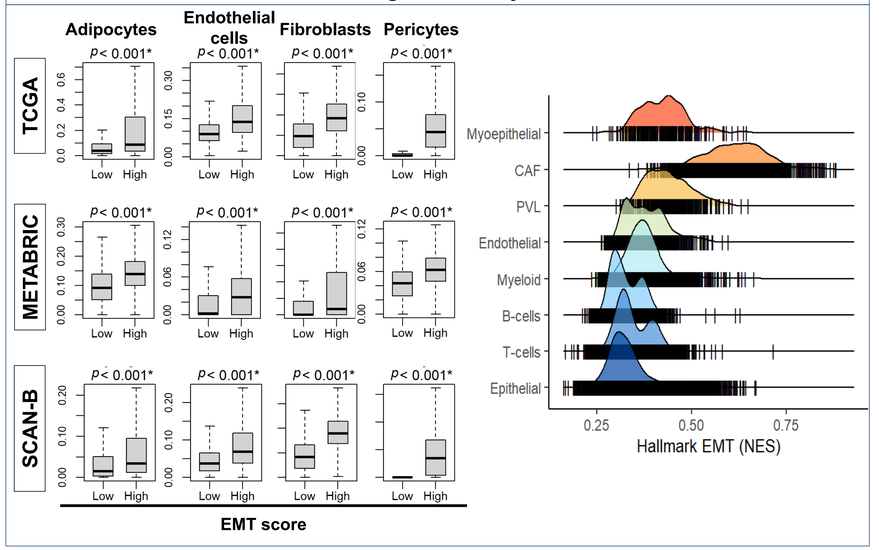
EMT-High Status Shows No Adverse Impact on DFS, DSS, or OS Across TCGA, METABRIC, and SCAN-B



EMT-High Tumors Show No Association With Mutation Load, Neoantigen Burden, or NAC Response



EMT-High Tumors Are Enriched for Stromal Components, With Cancer-Associated Fibroblasts Showing the Highest EMT Activity in Single-Cell Analysis



Reference

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Conclusion

Our findings suggest that EMT signal from transcriptome of a bulk tumor largely represent stromal components, particularly CAFs, rather than intrinsic EMT activity in malignant cells. This highlights the need for analyses of single-cell resolution to accurately interpret EMT biology in the tumor microenvironment.

COI and Contact Information

COI: All the authors declare no conflict of interest

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