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Unraveling the Immune-Metabolic Landscape to Inform Response Prediction for Neoadjuvant Chemotherapy in Triple-Negative Breast Cancer

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Introduction

Triple-negative breast cancer (TNBC) exhibits significant heterogeneity, and current neoadjuvant chemotherapy achieves pathological complete response (pCR) in only 40–60% of patients[1-5], highlighting an unmet need for predictive biomarkers. To address this, we conducted transcriptomic profiling on paired pre- and post-treatment samples from TNBC patients in the NeoPATH trial, who received neoadjuvant nab-paclitaxel and carboplatin. Our study aims to identify molecular features predictive of pCR, construct a robust immune-metabolic signature to guide chemotherapy selection, and uncover resistance mechanisms in residual tumors to inform post-neoadjuvant therapy.

Methods and Materials

Patient Cohort

This study analyzed the TNBC subset (n=74) of the prospective NeoPATH trial (NCT03907800), which evaluated neoadjuvant nab-paclitaxel plus carboplatin in high-risk TNBC or HER2-positive breast cancer. Pathological complete response (pCR) was defined as ypT0/Tis ypN0.

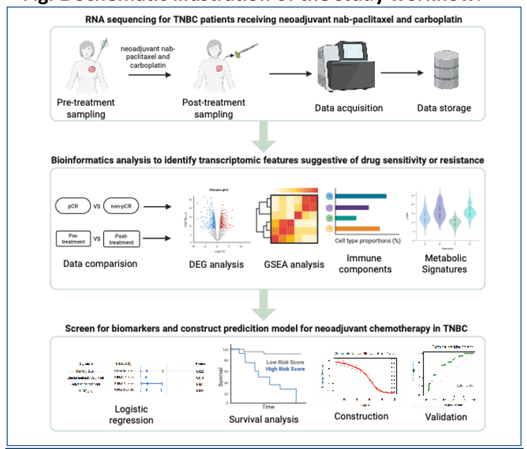
Transcriptomic Profiling and Analysis

Formalin-fixed paraffin-embedded (FFPE) tumor samples (pre- and post-treatment) were collected from TNBC patients for RNA sequencing. Gene set enrichment analysis (GSEA) and single-sample GSEA (ssGSEA) was used. Immune cell infiltration was estimated using published gene sets.

Predictive Modeling & Validation

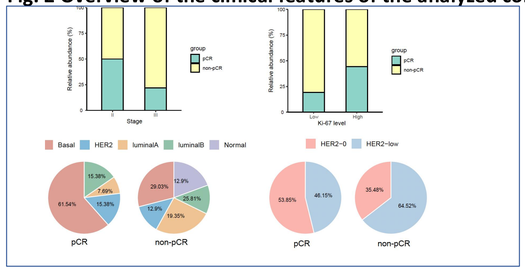
A predictive signature was constructed using LASSO-penalized logistic regression based on immune- and metabolism-related genes. Model performance was evaluated using ROC curves and AUC values, with external validation in two independent TNBC cohorts (GSE164458, GSE163882).

Fig. 1 Schematic illustration of the study workflow.



Results

Fig. 2 Overview of the clinical features of the analyzed cohort



Among the pCR patients, basal-like tumors constituted the majority with the percentage of 61.5%. Among patients with non-pCR, the HER2-low tumors accounting for the majority, with the percentage of 64.5%.

Fig. 3 Tumor immune states across patients with different responses.

A) The relative abundance of immune cell subsets across pre-treatment samples B) The ssGSEA enrichment scores of immune-related signatures.

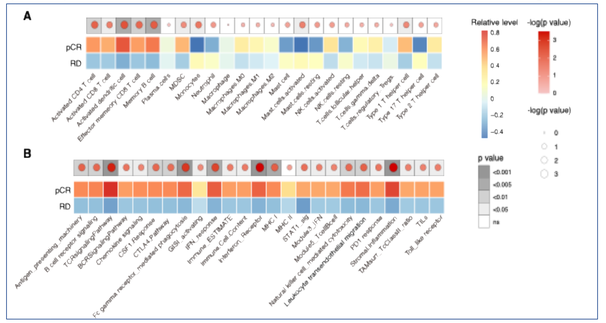
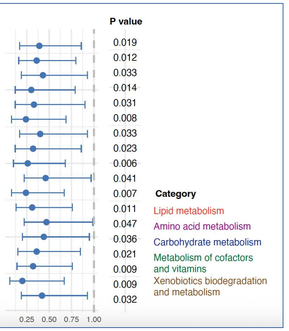


Fig. 4 The Association of metabolic signatures with treatment response.

Signatures	OR(95%CI)	P value	Category
Retinol metabolism	0.39(0.17–0.86)	0.019	
Porphyrin and chlorophyll metabolism	0.36(0.16–0.80)	0.012	
Folate biosynthesis	0.43(0.19–0.93)	0.033	
Drug metabolism – cytochrome P450	0.30(0.12–0.79)	0.014	
Butanoate metabolism	0.33(0.12–0.90)	0.031	
Ascorbate and aldarate metabolism	0.24(0.08–0.69)	0.008	
Tyrosine metabolism	0.40(0.17–0.93)	0.033	
Taurine and hypotaurine metabolism	0.32(0.12–0.86)	0.023	
Glycine,serine and threonine metabolism	0.26(0.10–0.68)	0.006	
Glutathione metabolism	0.46(0.22–0.97)	0.041	
Steroid hormone biosynthesis	0.24(0.08–0.67)	0.007	Lipid metabolism
Primary bile acid biosynthesis	0.31(0.13–0.76)	0.011	Amino acid metabolism
Glycosphingolipid biosynthesis – ganglio series	0.47(0.22–0.99)	0.047	Carbohydrate metabolism
Glycerophospholipid metabolism	0.44(0.20–0.95)	0.036	Metabolism of cofactors and vitamins
Glycerolipid metabolism	0.36(0.15–0.85)	0.021	Xenobiotics biodegradation and metabolism
Fatty acid elongation	0.32(0.14–0.76)	0.009	
Biosynthesis of unsaturated fatty acids	0.20(0.06–0.67)	0.009	
alpha Linolenic acid metabolism	0.42(0.19–0.93)	0.032	



Tumors having pCR presented higher infiltrations of activated CD4+ cells, CD8+ cells, dendritic cells, effector memory CD8+ T cells and memory B cells, suggesting active anti-tumor immune microenvironment. Tumors with residual disease (RD) harbored a globally lower scores of literature-defined immune signatures . RD samples had distinct metabolic characteristics of high energy production featured by active lipid metabolism and animo acid metabolism.

Fig. 5 Inferred immune cell infiltration level in pre- and post-treatment group

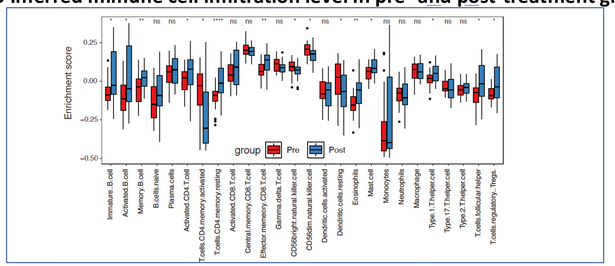
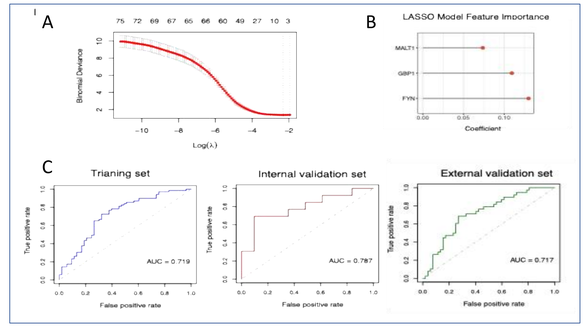


Fig. 6 Construction of the immuno-metabolic predictive signature

A) Variable selection using LASSO regression
B) Coefficients of the selected genes in the predictive signature
C) ROC in training set, internal validation set and external validation set.



Conclusions

To conclude, this study revealed that patients achieving pCR had upregulated signatures related to immune activation and downregulated metabolic signatures, based on which immune-metabolic predictive signatures for NAC benefit were constructed and validated. In addition, the results showed that tumor immune microenvironment had positive response for NAC which may potentize immunotherapy.

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