Neutrophil extracellular traps (NETs) signature to predict pathological complete response (pCR) in patients with triple negative breast cancer (TNBC) after neoadjuvant systemic therapy

Takeo Fujii[1,2], Jina Kim[3], Sungyong You[3], Hideki Furuya[4], Motoo Nomura[2], Manabu Muto[2]

1. Women's Malignancies Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, 2. Department of Medical Oncology, Kyoto University Graduate School of Medicine, Kyoto, Japan
3. Department of Urology and Department of computational Biomedicine, Cedars-Sinai Medical Center, Los Angeles, CA, USA, 4. Department of Biomedical Sciences, Cedars-Sinai Medical Center, Los Angeles, CA, USA

Background

- pCR after neoadjuvant therapy (NAT) in TNBC is associated with better prognosis.
- pCR is a key endpoint in neoadjuvant TNBC clinical trials.
- Identifying patients unlikely to achieve pCR is critical for optimizing NAT.
- Neutrophils are the most abundant in tumor microenvironment and form neutrophil extracellular traps (NETs).
- NETs have a context-dependent tumor- promoting or suppressing role.

Hypothesis

- NET-related gene signature stratifies patients into high vs low likelihood of pCR in TNBC.

Primary objective

- To develop a transcriptomic-based NET signature to predict pCR in TNBC.

Method and Materials

Identifying candidate genes associated with pCR among 131 previously reported NET-related genes (GSE 123845)
Differentially expressed genes (DEGs) between pCR and non-pCR (FDR<0.1, log2 fold change≥0.3)

Developing **transcriptome-based TNBC-NET score**

- External validation of the association between TNBC-NET score and pCR (GSE164458).
- Logistic regression model to assess the association between the TNBC-NET score and pCR.
- Gene set enrichment analysis (GSEA) to identify pathways significantly enriched between high and low TNBC-NET score groups.

Results

TNF	SELPLG	PTAFR	RIPK3
ITGB2	FPR1	LILRB2	TLR8
CXCL9	LAMP3	GZMB	CXCL11
CXCR6	HLA-A	HLA-B	MICB

16 NET-related genes upregulated in pCR (GSE123845)

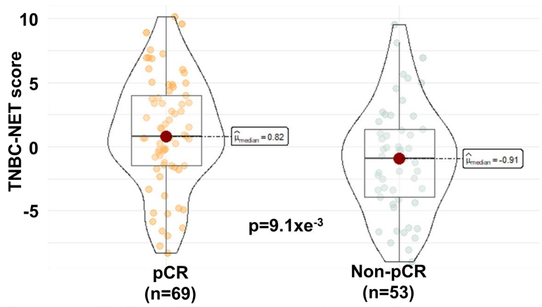


Figure 1. TNBC-NET score is high in pCR group in an independent cohort (GSE164458)

	Odds ratio	95% CI	p-value
TNBC NET-score			
Low			REF
High	5.59	1.1-28.5	0.04
Age	0.92	0.08-1.04	0.19
Menopausal status			
Perimenopause			REF
Post menopause	5.3	0.4-70	0.21
Ki-67	1.0	0.98-1.02	0.99
Clinical Stage			
Stage I			REF
Stage II	5.44	0.27-110.1	
Stage III	1.25	0.07-21.67	0.88

Multivariate logistic regression model to assess association with pCR

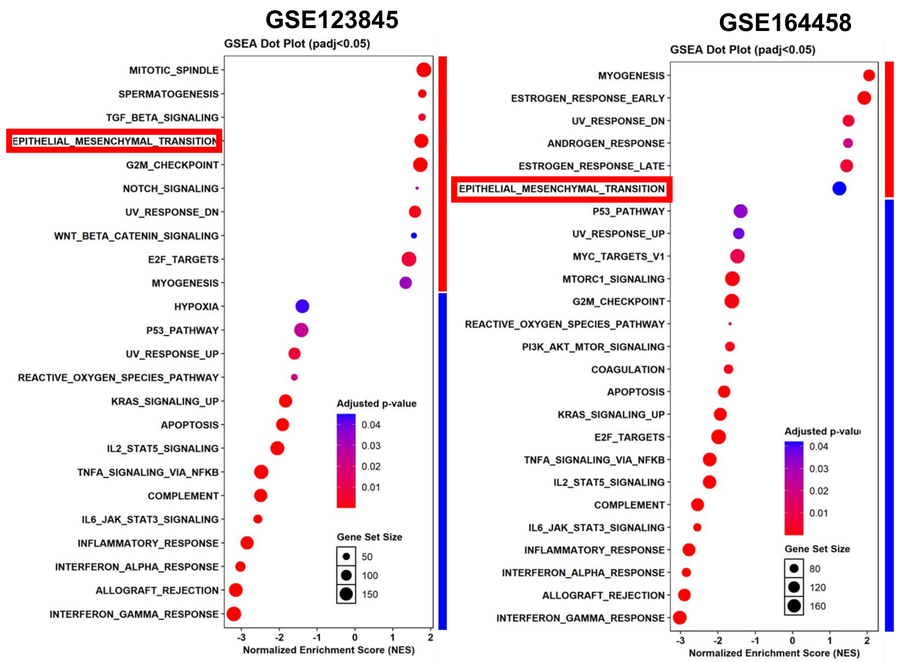


Figure 2. Enriched pathways in low TNBC-NET-score group compared to high score group

Summary and future direction

- Transcriptomics-based TNBC-NET score was developed and validated.
- Low TNBC-NET score was associated with low pCR rate.
- EMT pathway was enriched in low TNBC-NET group, suggesting a potential role in systemic therapy resistance.
- TNBC-NET score may serve as a biomarker to guide risk-adapted treatment aimed at improving pCR rates.
- Prospective studies are warranted.
- Experiments to understand resistance mechanisms in TNBC-NET score low group are ongoing.

Contact: Takeo Fujii, MD, MPH, takeo.fujii@nih.gov

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