Distinct Immune Landscapes in Inflammatory and Metaplastic Breast Cancer: Insights from Transcriptomic Profiling

E. R. Lopez[1], A. Nasrazadani[2], O. Baranov[3], V. Smirnov[3], A. Love[3], F. Paradiso[3], M. Hensley[3], R. Layman[2], J. Mouabbi[2], C. Yam[2], B. Nelson[2], The MDACC Inflammatory Breast Cancer Team, S. H. Giordano[2], J. K. Litton[2], B. Lim[2]

[1]Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA [2]Department of Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA [3]BostonGene Corporation, Waltham, MA, USA [4]MDACC Inflammatory Breast Cancer (MDACC-IBC) Team, The University of Texas MD Anderson Cancer Center, Houston, TX, USA.

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center — Making Cancer History®

Introduction

Background: Inflammatory breast cancer (IBC) and metaplastic breast cancer (MpBC) are rare subtypes associated with poor prognosis and limited therapeutic targets.

Aim: To characterize distinct features of IBC and MpBC by performing a comparative immune transcriptomic analysis of IBC and MpBC tumors using a large institutional dataset.

Methods

- 341 institutional breast cancer samples were evaluated using BostonGene's comprehensive AI-driven transcriptomic analysis platform.
- Gene expression profiling was conducted using a panel of 504 cancer and immune-related genes, including key immune checkpoint regulators (PD-L1/CD274), epithelial-mesenchymal transition (EMT) markers, and antibody-drug conjugate (ADC) targets such as TROP2 (TACSTD2).
- Pathway-level differences were assessed using Gene Set Expression Analysis (GSEA).
- Immune cell typing was performed based on bulk RNA-seq data using Kassandra cell deconvolution algorithm.

Figure 1. Summary of Transcriptomic Analysis Cohort

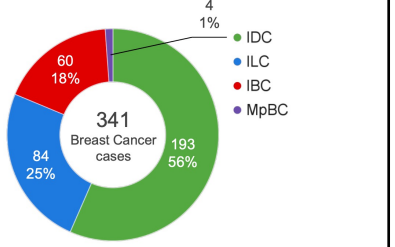


Fig. 1: Institutional cohort consisting of four breast cancer subtypes: Invasive ductal carcinoma (IDC), invasive lobular carcinoma (ILC), inflammatory breast cancer (IBC), and metaplastic breast cancer (MpBC).

Results

Figure 2. Alteration Cross-Comparison

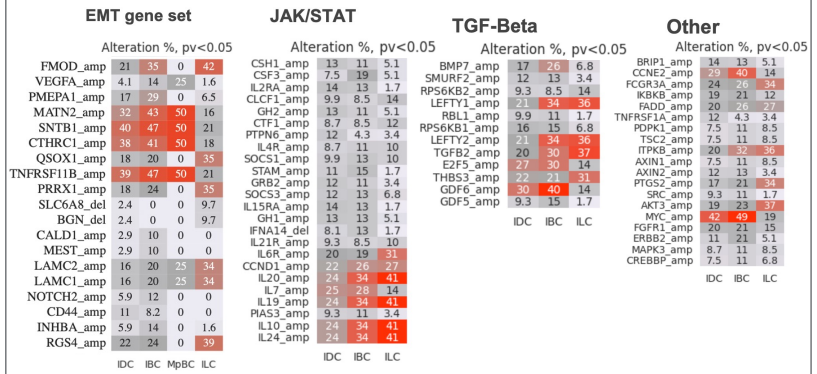


Fig. 2: Pathway-level difference analysis of gene expression was conducted using Gene Set Expression Analysis (GSEA). **Due to the small MpBC sample size, findings reflect biological trends rather than statistically powered comparisons.*

Figure 3. Expression of Key Breast Cancer Genes

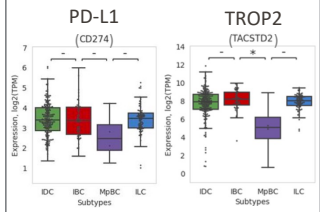


Fig. 3: Transcriptomic expression of PD-L1 (CD274) and TROP2 (TACSTD2) across four breast cancer subtypes.

Figure 4. Cell Deconvolution Medians

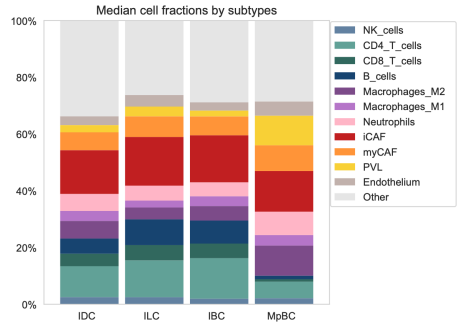


Fig. 4: Median cell proportions and distributions as determined by Kassandra cell deconvolution algorithm.

Figure 5. Cell Deconvolution Distribution in Breast Cancer Subtypes

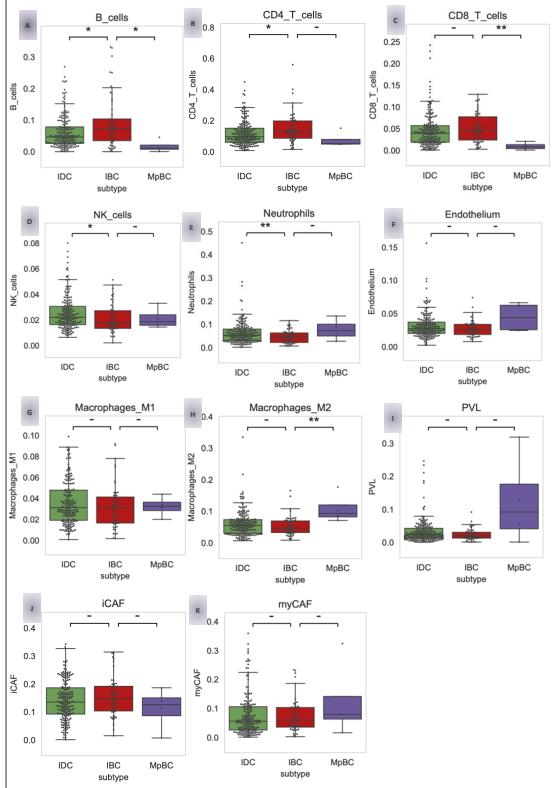


Fig. 5: Comparison of breast cancer subtypes by populations of B-cells **(A,B)**, T-cells **(C)**, Natural Killer (NK) Cells **(D)**, Neutrophils **(E)**, Endothelial cells **(F)**, Macrophages **(G,H)**, Perivascular Lymphocytes (PVL) **(I)**, and Cancer-Associated Fibroblasts (CAF) **(J, K)**.

Results

I. Transcriptomic / Pathway Analysis

- IBC showed upregulation of JAK/STAT signaling, consistent with an inflamed tumor microenvironment.
- MpBC tumors were enriched for epithelial–mesenchymal transition (EMT) signatures.

II. Immune Checkpoint & Target Expression

- PD-L1 (CD274) expression:
  - No significant differences between IBC and IDC.
  - Low in MpBC, though not statistically significant due to limited sample size.
- TROP2 (TACSTD2) expression:
  - Elevated in both IBC and MpBC.
  - MpBC displayed lower overall expression and greater heterogeneity compared to IBC.

III. Immune Cell Deconvolution

- Compared to IDC, IBC demonstrated:
  - ↑ CD4 T cells ($p < 0.05$)
  - ↑ B cells ($p < 0.05$)
  - ↓ NK cells ($p < 0.05$)
  - ↓ Neutrophils ($p < 0.05$)
- Compared to IDC, MpBC exhibited:
  - ↓ CD8 T-cell infiltration relative to both IDC and IBC ($p < 0.05$).
  - ↑ M2 macrophage abundance ($p<0.05$), suggesting ↑ immunosuppression.
  - Trends toward ↑ perivascular lymphocytes (PVL) and endothelial signatures, not statistically significant.

Conclusions & Limitations

Findings suggest:

- IBC = inflamed phenotype with altered effector cell balance.
- MpBC = reduced cytotoxic infiltration + enhanced immunosuppressive myeloid features.
- IBC may benefit from ICIs when PD-L1 or T-cell infiltration is present, whereas MpBC may require combination strategies to overcome EMT-mediated immune suppression.

Findings are hypothesis generating, and future validation studies are needed.

Results must be interpreted with caution due to the small MpBC cohort (n = 4).

MDACC Inflammatory Breast Cancer (MDACC-IBC) Team Authorship Contributors:

Rachel Layman[1], Bora Lim[1], Azadeh Nasrazadani[1], Sadia Saleem[1], Vicente Valero[1], Michael C. Stauder[2], Wendy A. Woodward[2], Anthony Lucci[3], Susie X. Sun[3], Gary J. Whitman[4], Miral Patel[4], Huong Le-Petross[4], Yang Lu[4], Angela Marx[1], Angela Alexander[1], Chasity Yajima[1], Megumi Kai[1], Lily Villarreal[1], Heather Lopez[1].

[1]Department of Breast Medical Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [2]Department of Breast Radiation Oncology, Division of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [3]Department of Breast Surgical

Acknowledgements

The transcriptomic analyses were performed via collaboration with BostonGene and Morgan Welch IBC Research and Clinic Program (MW IBC program). MW IBC program is funded by the State of Texas Rare and Aggressive Breast Cancer Grant.