Integrated Tumor Microenvironment Profiling Reveals Distinct Immune, Stromal and MicroRNA Signatures Across Triple Negative Breast Cancer Molecular Subtypes

Shivangi Sengupta[1,2] Baidehi Maiti, MD, PhD[1,3]

[1]Fairview Hospital, Cleveland Clinic, Cleveland, OH, [2]College of Arts and Sciences, Case Western Reserve University, OH [3]Moll Cancer Center, Cleveland Clinic, Cleveland, OH

SAN ANTONIO BREAST CANCER SYMPOSIUM®
DECEMBER 10–13, 2024
SABCS.ORG

Introduction

The breast tumor microenvironment is influenced by miRNAs, which can act as biomarkers for cancer subtyping, detection, and treatment. However, the relationship between microenvironment and miRNA in TNBC molecular subtypes is underexplored. We hypothesized that there are subtype-specific cell enrichment patterns, whose heterogeneity is reflected in immunomodulatory and stroma-modulatory miRNA expression diversity.

Methods and Materials

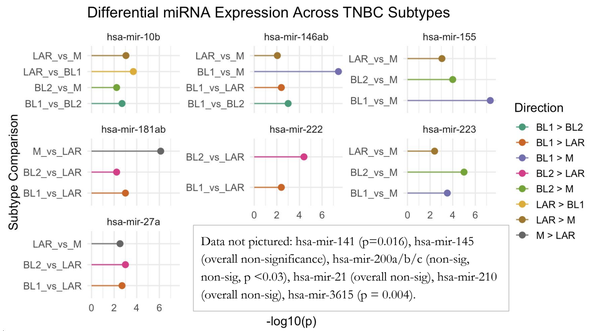
Normalized gene expression data was analyzed for TCGA, METABRIC, and GSE31519 cohorts. Normalized MiRNA sequencing data (ppm) was obtained for TCGA. TNBCType was used to classify cases as basal-like 1 (BL1), basal-like 2 (BL2), luminal androgen receptor (LAR) and mesenchymal (M). XCell 2.0 computed immune and stromal enrichment. For TCGA, normalized miRNA findings were integrated with XCell results through correlates. Kruskal-Wallis tests, Bonferroni correction, and Dunn's tests were performed with R.

Results

Across cohorts, (n = 1038; n = 195 validation), TNBC subtypes showed heterogeneity in stromal ($p < 0.000001$), immune ($p < 0.00001$) and microenvironment scores ($p = 2.59e-8$). BL1 had enriched CD8+ T, NK and dendritic cells. BL2 exhibited elevated epithelial cells, neutrophils and M2-like macrophages ($p < 0.01$). M was marked by low T-cells, and high mesenchymal stromal cells. LAR had enriched B ($p < 0.01$) and plasma cells. The TCGA cohort (n = 175) showed differential composition in 13/15 tested cell types: adipocyte, endothelial, CD8+ T, CD4+ T, M1 macrophage, M2 macrophage, NK, B, dendritic, neutrophil, monocyte, mast (all $p < 0.001$), and fibroblast ($p = 0.008$). There was expression variation across subtypes for 12/17 profiled miRNAs (Table): miR-10b, miR-146a/b, miR-155, miR-181a-1/2, miR-222, and miR-223: ($p < 0.001$); miR-141: ($p = 0.016$); miR-27a: ($p = 0.003$); and miR-3615: ($p = 0.004$). MiR-155 and miR-146a/b correlated positively with immune scores, CD8+ T cells, and M1 macrophages. Elevated miR-146a was found in BL1 compared to M, consistent with miR-146a status as an epithelial-to-mesenchymal transition (EMT) inhibitor. High miR-146a/b expression in BL2 reflected inflammatory modulation, and lower levels in M may allow for EMT. High miR-155 expression in BL1 aligned with the immune-enriched phenotype. EMT promoters, miR-181a-1 and miR-181a-2, were elevated in M. Elevated miR-222 and miR-223 in BL2 correlated with immune enrichment. MiR-200a/b levels did not significantly differ across subtypes, consistent with their shared epithelial features.

miRNA	Known Function	Expression Diversity Across Subtypes	Relative Expression Between Subtypes
hsa-mir-10bv	Promotes EMT, metastasis	$p < 0.001$	LAR > M ($p = 0.0009$). BL2 > M ($p = 0.006$). LAR > BL1 ($p = 0.0002$). BL1 > BL2 ($p = 0.002$).
hsa-mir-146a/b	Anti-inflammatory; NF-κB regulator	$p < 0.001$	BL1 > M ($p = 3.57e-8$). BL1 > LAR ($p = 0.004$). BLI > BL2 ($p = 0.001$). LAR > M ($p = 0.009$).
hsa-mir-155	Pro-inflammatory; immune cell activator	$p < 0.001$	LAR > M ($p = 0.0009$). BL1 > M ($p = 4.76e-8$). M < BL2 ($p = 0.0001$).
hsa-mir-181a-1/2	T cell sensitivity enhancer; isoforms mir-181a-1 and mir4-181b-2.	$p < 0.001$	M > LAR ($p = 7.55e-7$). LAR < BL1 ($p = 0.001$). LAR < BL2 ($p = 0.006$).
hsa-mir-222	Known oncomiR; affects proliferation, immune evasion	$p < 0.001$	BL2 > LAR ($p = 0.00004$). BL1 > LAR ($p = 0.004$).
hsa-mir-223	Myeloid cell regulator (macrophage, neutrophil)	$p < 0.001$	BL2 > M ($p = 0.00001$). BL1 > M ($p = 0.0003$). LAR > M ($p = 0.004$).
hsa-mir-27a	Angiogenesis and EMT regulation	$p = 0.003$	LAR < M ($p = 0.003$). BL1 > LAR ($p = 0.002$). BL2 > LAR ($p = 0.001$).

Graphs



Conclusions

Using the largest public miRNA-seq dataset, this study provides novel mechanistic insight into the TNBC microenvironment and reveals promising miRNA biomarkers: miR-146a for BL1, miR-146b and miR-222 for BL2, miR-3615 for BL 1/2, miR-10b for LAR, miR-181a/b for M, low miR-223 for M (Table & Graph). These findings have potential for both diagnostic and therapeutic implications.

Further Research

Further research may seek to validate the subtype-specific miRNA signatures identified here in independent patient cohorts and functional assays. Investigating regulatory mechanisms, direct molecular targets, and therapeutic modulation of miRNA of interest can further clarify their role in TNBC subtype biology and their influence on immune and stromal cell composition of TNBC.

Contact:
Shivangi Sengupta
Case Western Reserve University
Email: sms481@case.edu

This presentation is the intellectual property of the Shivangi Sengupta. Contact them at sms481@case.edu for permission to reprint and/or distribute.

© Poster Template by Genigraphics® 1.800.790.4001 www.genigraphics.com