Comparison of immune microenvironment between primary and metastatic breast tumors

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Introduction

• Immune evasion has been described as one of the mechanisms by which cancer cells gain the ability to metastasize from the primary tumor to distant sites in the body.1
• In triple-negative breast cancer (TNBC), metastatic tumors are shown to be more immunologically silent than primary tumors. As a result, there are varying degrees of responses to immunotherapy between early-stage and metastatic TNBC.2
• Positive clinical responses to immune checkpoint inhibitors (ICIs) are seen in patients with early-stage TNBC regardless of PD-L1 expression, whereas greater benefits to ICIs are seen in metastatic TNBC with higher PD-L1 expression.3
• In this study, we investigated the differences in the immune signatures of primary and metastatic breast cancer in a real-world patient population.

Methods

• A retrospective cohort of 529 breast tumors tested in the real-world clinical setting were evaluated by comprehensive genomic and immune profiling (CGIP) of the tumor microenvironment (Figure 1).
• Tumor specimens were classified as primary breast, any lymph nodes (regional and non-regional) or metastatic visceral sites. Lymph node samples were chosen as positive controls due to expected elevated inflammatory signaling.

Figure 1. CGIP methods description.

• Over-representation and proportion analysis using chi-squared test was applied to determine the association of specimen sites to various genomic and immune correlates.

Genomic Profiling

SNV/INDEL/Fusion/CNV for 523 genes
Tumor mutational burden (TMB)
Microsatellite Instability (MSI)
• RNA-seq expression profiling of 395 immune transcripts4
• PD-L1 IHC4
• Cell Proliferation1
• Tumor Inflammation5

Figure 2. Tumor immunogenic score (TIGS) distributions by sample source: A) TIGS group prevalence in each sample source with total patient number in each group indicated; B) TIGS score distribution in each sample source group. Wilcoxon Rank Sum p values indicated.

Results

Tumor inflammation landscape
Samples of primary breast lesions harbored a greater degree of immune infiltration, demonstrating a higher TIGS score than metastatic visceral lesions (p=4.4x10^-7).

Future Directions for Research:

• Although further clinical validation of these immune biomarkers is required, this study demonstrates the potential for CGIP to provide immunotherapy treatment decision support when selecting an ICI in metastatic breast cancer.
• Combination treatments of ICIs with chemotherapy, targeted therapies or cancer vaccines may be promising therapeutic approaches to enhance the immune responses and potentially overcome resistance to ICIs in metastatic breast cancer.

Figure 3. PD-L1 IHC group (Positive >10% CPS in each sample source with total patient number in each group indicated).

Biomarkers of response to checkpoint inhibitors
Primary lesions also demonstrated a greater proportion of PD-L1 positive tumors than metastatic lesions (44% vs 21%, p < 0.001) and higher expressions of other immune checkpoints such as TIGIT (p<0.001), LAG3 (p=0.037) and TIM3 (p<0.001).

Figure 4. Box plots showing gene expression (S2DE) rank distributions of TIGIT (A), LAG3 (B), and TIM3 (C) in each sample source group. Wilcoxon Rank Sum p values shown.

Table 1. Cohort characteristics.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>N (%)</th>
</tr>
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<tbody>
<tr>
<td>Age</td>
<td>Median: 63.2 years, Range: 25.5-93.5 years</td>
<td>529 (100%)</td>
</tr>
<tr>
<td>Gender</td>
<td>Female</td>
<td>519 (98%)</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>10 (1.9%)</td>
</tr>
<tr>
<td>Sample Source</td>
<td>Lymph node</td>
<td>72 (14%)</td>
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<tr>
<td></td>
<td>Metastatic</td>
<td>232 (44%)</td>
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<tr>
<td></td>
<td>Primary breast</td>
<td>224 (42%)</td>
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<tr>
<td>Tumor Histology</td>
<td>Invasive ductal carcinoma, NOS</td>
<td>287 (54%)</td>
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<tr>
<td></td>
<td>Invasive lobular carcinoma</td>
<td>26 (4.9%)</td>
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<td></td>
<td>Mammary adenocarcinoma, NOS</td>
<td>207 (39%)</td>
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<tr>
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<td>Other</td>
<td>10 (1.9%)</td>
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<tr>
<td>All Samples</td>
<td>529 (100%)</td>
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</tbody>
</table>

References


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